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VITAMIN A AND KERATINIZATION

STUDIES ON THE HAMSTER CHEEKPOUCH

DONALD J. LAWRENCE, A.B.
HOWARD A. BERN, PH.D.
MONTE G. STEADMAN, M.D.
BERKELEY, CALIF.
SAN FRANCISCO, CALIF.

Oral leukoplakia in man, the lesion wherein normally parakeratotic epithelium undergoes keratinizing metaplasia,[11,27] has been treated with vitamin A trochees.[15] In general, improvement has been reported; however, little is known concerning the mode of action or the precise histologic effects of such treatment.

The ability of high concentrations of vitamin A to produce mucous metaplasia of certain normally keratinizing epithelia is well established both *in vitro*[5,26] and in intraocular transplantation studies.[8] Although the vitamin is considered to have a specific effect—stimulation of mitosis—on rodent epidermis *in vivo* at low dose levels,[9] it has been pointed out[2,9,14] that there is little direct evidence from studies on laboratory animals to support a specific antikeratinizing effect of the vitamin when applied topically *in vivo*. In man, local application

From the Department of Zoology and its Cancer Research Genetics Laboratory, University of California, Berkeley, and the Department of Otolaryngology, Kaiser Foundation Hospital, San Francisco, California.

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of the vitamin in a limited number of vehicles has been reported to have no effect.[6]

The cheekpouch epithelium (described briefly by Salley[18]) of the golden hamster (*Mesocricetus auratus*) is a typical "soft"-keratinizing epithelium[1,10] with a narrow but definite stratum granulosum and an eosinophilic, desquamating stratum corneum; in general, normal hamster cheekpouch epithelium resembles somewhat the lesion of leukoplakia of human oral epithelium both histologically and embryologically.[7,16]

In order to determine the response of hamster cheekpouch epithelium under controlled conditions to various levels of locally-applied vitamin A, the experiments described herein were undertaken. In addition, the effects of a comparable amount of oleic acid, considered to be a "nonspecific irritant" of certain keratinizing epithelia,[13] are reported.

MATERIALS AND METHODS

Preliminary Experiments. Thirty-seven male hamsters were employed in preliminary experiments, wherein various pellet bases and vehicles were tested in order to find a material with a minimum effect on cheekpouch epithelium. Various embedding paraffins, vaseline-paraffin mixtures, and commercial vitamin A trochees were tested; all produced at least a moderate degree of epithelial hypertrophy, except the carrier mixture finally employed in the definitive experimental series. In addition, various dose levels of vitamin A (both the concentrate of natural esters from fish liver oil, as well as the crystalline synthetic alcohol) were tested, with the crystalline synthetic form of the vitamin employed in the definitive experiments.

In another preliminary experiment, pellets containing oleic acid (without vehicle) in an amount equivalent in moles to about 10^6 i.u. of vitamin A, inserted into the cheekpouch for ten days, produced moderate epithelial hypertrophy accompanied by a prominent stratum granulosum and a thick stratum corneum. Accordingly, in the hamster cheekpouch, as in mouse epidermis,[9] massive amounts of oleic acid will produce epithelial hypertrophy.

Pellets. Various amounts of vitamin A or of oleic acid were dissolved in diethyl ether (0.13 ml/pellet), which was then mixed with light mineral oil USP (0.13 ml/pellet). The resulting mixture was added to melted paraffin (Bioloid, MP 43-46° C.), cast in 8 mm glass test tubes, and chilled in a freezing compartment at 0° C. During

mixing with warm paraffin, the ether appeared to boil off. The resulting paraffin rods were divided into pellets weighing 1.3 ± 0.05 g. These pellets were stored in the dark at 0° C., and were used within ten hours. In certain control groups, pellets without vitamin A or oleic acid, and with or without the ether-mineral oil vehicle (groups 3 and 2, respectively), were tested. In one group (group 12), commercial trochees containing 1.5×10^5 i.u. of vitamin A were used in place of the paraffin pellets.

Animals. Sixty-nine male golden hamsters, obtained at 2½ to 3½ months of age from a local dealer, were employed in the experiments reported below. Animals were housed 2 to 3 per cage, and fed Purina rabbit pellets, fresh greens, and tap water *ad libitum*. Within five to seven days after receipt, animals were anesthetized by intraperitoneal injection of sodium pentobarbital solution, 0.6 mg/kg body weight.[12] The mucosa of the right cheekpouch was everted with fine forceps and cleaned of debris with a gentle stream of saline and light strokes of a cotton-tipped applicator moistened in saline. The right pouch was then replaced. A full-thickness skin incision, 1.5 to 2 cm long, was made approvimately 1.5 cm posterior to the right labial commissure at right angles to the major pouch axis, exposing the freed submucosal surface of the right pouch. After insertion of a pellet through the pouch mouth, the right pouch was loosely tied off through the skin incision by a single loop of heavy cotton thread placed around the pouch anterior to the pellet. The skin incision was closed separately by four or five interrupted sutures of heavy cotton thread, and gentian violet in parlodion was applied to the closed skin incision. The left pouch remained unoperated to control for any systemic effects of the pellet.

At the end of the treatment period, hamsters were sacrificed with ether; both cheekpouches were removed, slit longitudinally to expose the mucosa, and flattened on thin cardboard with the mucosa uppermost. Portions of the pouch, after dipping briefly in 70% ethanol as a wetting agent, were fixed in Bouin's fluid. Paraffin sections were cut at 7 μ (and in some cases also at 3 μ) and stained with hematoxylin and eosin (H. & E.). Adjacent paraffin sections were treated with the periodic acid-Schiff (PAS) reaction with and without prior exposure to buffered animal diastase (and, in some cases, also to buffered malt diastase, a mixture of animal and malt diastases, or human saliva); a light nuclear stain with hemtoxylin was usually added to the PAS-treated sections.

H. & E.-stained sections of each cheekpouch specimen were measured at 20 adjacent areas (at points separated by about 150 μ) with

TABLE I

EFFECT OF 10 DAYS' TREATMENT WITH VITAMIN A ON EPITHELIAL THICKNESS OF HAMSTER CHEEKPOUCH MUCOSA

					RIGHT POUCH EPITHELIAL THICKNESS IN μ (MEAN ± S.E.m)				
						STATISTICAL EVALUATION				
GROUP	NO. OF HAMSTERS	PELLET	VEHICLE	VITAMIN A (I.u./pellet)	SUBCORNEAL LAYERS (a)	P	Compared with Group	STRATUM GRANULOSUM	STRATUM CORNEUM (b)	OVERALL EPITHELIUM (a + b)
1	6	(Untreated Control)			28.6±0.9	N.S.*	1L†	3.0	4.6	33.2±1.1
2	5	Paraffin	—	—	20.9±1.1	<.001	2L	2.2	4.6	25.5±1.7
						<.001	1R			
3	10	Paraffin	E-MOL‡	—	22.6±0.8	<.001	3L	2.4	5.4	28.0±0.8
						<.001	1R			
						N.S.	2R			
4	6	Paraffin	E-MOL	Oleic Acid§	25.8±2.0	N.S.	3R	3.5	6.4	32.2±2.5
5	6	Paraffin	E-MOL	10^2	37.5±3.4	<.001	3R	12.0	6.4	43.9±4.5
6	5	Paraffin	E-MOL	5×10^2	48.7±5.1	<.001	3R	8.6	7.9	56.6±5.3
7	5	Paraffin	E-MOL	10^3	64.5±3.0	<.001	3R	10.0	5.9	70.4±1.3
8	6	Paraffin	E-MOL	10^4	53.1±7.0	<.001	3R	0.3	0.4	53.5±6.5
9	6	Paraffin	E-MOL	2.5×10^4	41.0±4.4	.01–.001	3R	0	0	41.0±4.4
10	6	Paraffin	E-MOL	5×10^4	38.7±2.2	<.001	3R	0	0	38.7±2.2
11	5	Paraffin	E-MOL	10^5	25.8±4.0	N.S.	3R	0	0	25.8±4.0
12	3	(Commercial vitamin A trochee)		1.5×10^5	0	—	—	0	0	0

TABLE I (Continued)

	LEFT POUCH EPITHELIAL THICKNESS IN μ (MEAN ± S.E.m)					
GROUP	SUBCORNEAL LAYERS (a)	STATISTICAL EVALUATION P	Compared with Group	STRATUM GRANULOSUM	STRATUM CORNEUM	OVERALL EPITHELIUM (a + b)
1	27.1±1.0	N.S.	1R†	2.9	5.4	32.5±0.9
2	30.5±0.1	N.S.	1L	3.0	3.9	34.5±0.9
3	27.4±0.2	N.S.	1L	2.4	4.9	32.3±0.9
4	34.0±1.5	.01–.001	3L	2.6	4.0	38.0±1.5
5	24.7±0.8	N.S.	3L	2.9	3.7	28.4±0.9
6	25.9±0.7	N.S.	3L	2.4	4.1	30.0±0.9
7	27.5±1.6	N.S.	3L	2.8	5.9	33.4±1.0
8	30.9±0.8	.01–.001	3L	3.1	7.5	38.4±1.7
9	30.1±0.7	.02–.01	3L	2.5	6.2	36.3±1.6
10	30.1±2.0	N.S.	3L	3.9	9.5	39.5±2.3
11	27.5±1.2	N.S.	3L	3.0	7.8	35.3±1.3
12		(not recorded)				

* N.S. = Not significant † L = Left pouch; R = Right pouch ‡ E-MOL = Ether-mineral oil mixture § Equivalent in moles to 10^5 vitamin A

an ocular micrometer at about 500 X magnification. Overall epithelial thickness, stratum corneum thickness, and stratum granulosum thickness were recorded. The thickness of the subcorneal epithelial layers was obtained by subtraction of the stratum corneum thickness from the overall epithelial thickness.

OBSERVATIONS

General Observations. Within a few hours, the originally cylindrical paraffin pellet assumed an ovoid form in conformation with the shape of the cheekpouch lumen. In general, hamsters bearing pellets were somewhat irritable, but apparently continued both to feed and to employ the left (unoperated) pouch for storage. At the highest dose levels of vitamin A employed, the area over the treated pouch appeared grossly inflamed and tender after two to three days, and these animals were obviously irritable and moderately debilitated. At the two lowest doses of vitamin A employed (as in both control pellet groups), no inflammation was visible grossly.

At autopsy, no change in the gross appearance of the pouch was noted in the control pellet groups (groups 2, 3), in the oleic acid group (group 4), or in the two lowest dose-level groups treated with vitamin A (groups 5, 6). In animals receiving larger amounts of vitamin A, inflammation of the pouch and a cloudy-appearing exudate between pouch and pellet, both present in degree roughly proportional to the amount of vitamin employed, were observed. In the group treated with vitamin A trochees, and in the group receiving the largest amount of vitamin A in paraffin, the inner pouch surface appeared to be composed at least in part of early granulation tissue.

Histology of Normal Mucosa. On microscopic examination, untreated control specimens (Fig. 2a) consisted of a submucosa of dermis-like connective tissue, 80-100 μ thick, containing a variable amount of striated muscle and with a well-defined, narrow basement membrane (visible with PAS technique). The submucosal tissue was covered by an epithelium of about 35 μ total thickness, which exhibited the histologic elements[1] characteristic of classic "soft" keratinization (*i.e.*, a loose, dry eosinophilic stratum corneum and a visible stratum granulosum). The stratum corneum appeared to remain fairly cohesive and intact, but was often separated along part of its length from the underlying epithelium. Untreated control epithelium usually contained small foci of 1 to 4 glycogen-laden cells in the subgranular (Malpighian) layers (Fig. 3b); such foci were located at

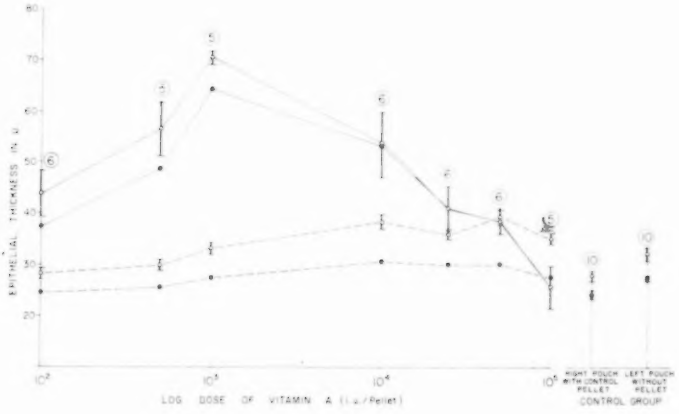
EPITHELIAL THICKNESS (IN μ)
LOG DOSE OF VITAMIN A (I.U./Pellet)
RIGHT POUCH WITH CONTROL PELLET
LEFT POUCH WITHOUT PELLET
CONTROL GROUP

Fig. 1.—Effect of ten days of treatment with vitamin A on epithelial thickness of hamster cheekpouch mucosa. Solid lines = right (treated) pouch; broken lines = left (untreated) pouch; open circles = overall epithelial thickness (with SEm indicated); solid circles = thickness of subcorneal layers; numbers in circles indicate number of animals per group.

intervals of 100 to 200 μ along the epithelium. No significant difference in thickness was observed between left and right pouch epithelium in the untreated group.

Effect of Control Pellets. In the pellet control groups (groups 2, 3), the right pouch epithelium was significantly reduced in thickness when compared either to the corresponding untreated left pouch epithelium or to the right pouch epithelium of untreated animals (group 1). There was no significant difference between the thickness of the right pouch of group 2 compared to the right pouch of group 3; therefore, it was concluded that the addition of the ether-oil vehicle had no significant effect over paraffin alone, and group 3 was adopted as the effective control group for subsequent comparisons. In groups 2 and 3, the right pouch (Fig. 2c) often exhibited ovoid epithelial nuclei in the basal and intermediate layers (in addition to the ovoid and flattened nuclei normally observed in the upper layers), with the major nuclear axis parallel to the basement membrane region. Glycogen was reduced or absent. The left (untreated) pouch epithelium was unchanged in appearance or thickness when compared to the left pouch epithelium of group 1.

Effect of Oleic Acid. Oleic acid (group 4) had no significant effect on the overall thickness of the right (treated) pouch epithelium (Fig. 3a). Minor changes included a small increase in thickness of stratum corneum, the presence of ovoid nuclei in the lower epithelial layers similar to those described in groups 2 and 3, an increase in size of some of the granules of stratum granulosum, and reduced or absent glycogen. The left pouch epithelium was slightly thicker when compared with the left pouch epithelium of group 3, but otherwise unchanged.

Effect of Vitamin A on Right (Treated) Pouch. At dose levels up to 10^3 i.u./pellet (groups 5 to 7) of vitamin A, the untreated pouch showed over-all thickening of the epithelium in degree roughly proportional to log dose (Fig. 1); such thickening was most marked in the subcorneal layers. The granular layer appeared thickened, and individual granules were markedly increased in size (Figs. 2c and 2d). Glycogen was reduced or absent in group 5, reduced in group 6, and of normal amount in group 7.

An apparent healing response (parakeratosis, absence of a stratum granulosum, increased glycogen) was observed at small foci in group 6 and more frequently in group 7. Such areas showed cells with accumulations of basophilic material in the lower region of the cytoplasm with non-staining clear upper cytoplasm; the clear upper areas only rarely contained demonstrable glycogen. When such atypical regions constituted more than about 5 to 10% of the total epithelium in any single specimen, they were included in measurements of various thicknesses.

Leukocyte invasion of the submucosa was rare or absent in group 5, slight in group 6, and moderate in group 7; leukocytes were rare or absent in the epithelium of groups 5 to 7, being observed only in some areas of parakeratosis with heavy glycogen deposition.

At higher dose levels of the vitamin, the average thickness of the stratum granulosum and of the stratum corneum was greatly reduced (group 8), or these layers were entirely absent (groups 9 to 11; Fig. 2d). Glycogen deposition was increased over that observed after smaller amounts of vitamin A, and was most marked in the surface layers. Leukocyte invasion of the outermost layers of the epithelium (but generally not of the intermediate layers and of the submucosa) was observed in groups 7 to 11.

In groups 10 and 11, but most frequently in group 11, epithelial downgrowths (Fig. 3f) were observed. Folding of the epithelium

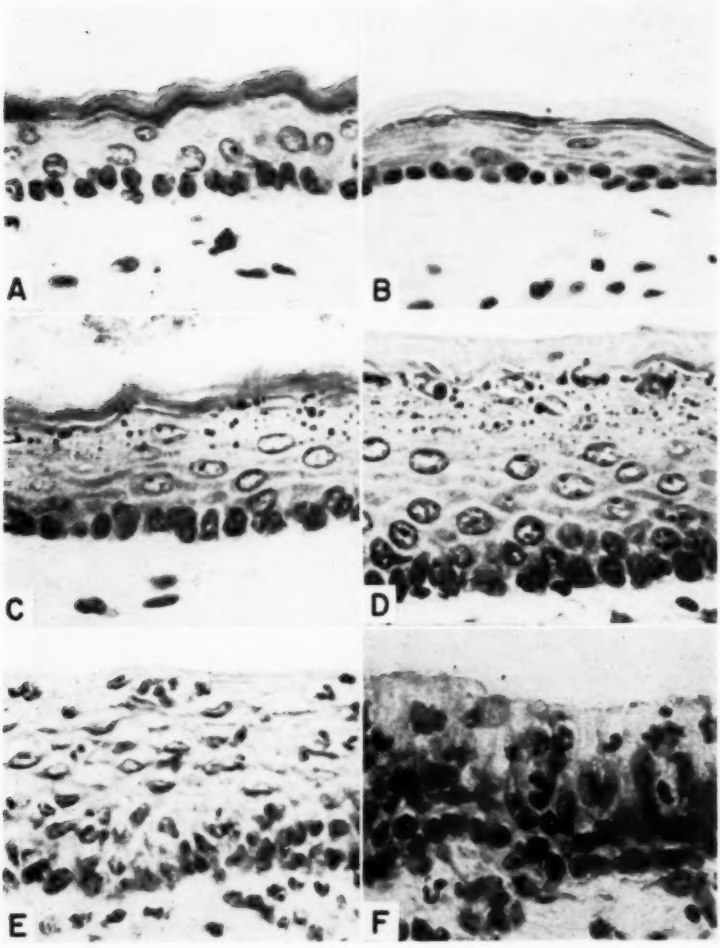

Fig. 2.—*A*. Untreated mucosa of hamster cheekpouch (group 1). Note presence of stratum corneum and fine granular layer. H.&E., X 870. *B*. Paraffin-vehicle control (right pouch, group 3). Note thinning of epithelium, suggestion of ovoid nuclei in lower layers. H.&E., X 870. *C*. Vitamin A, 10^2 i.u./pellet (group 5). Note thicker epithelium, thicker granular layer, and presence of stratum corneum. Compare size of individual keratohyalin granules with those of Figures 2 *A* and *B*. H.&E., X 870. *D*. Vitamin A, 10^3 i.u./pellet (group 7). Note epithelial hypertrophy, enlarged keratohyalin granules, presence of stratum corneum. H.&E., X 870. *E*. Vitamin A, 10^4 i.u./pellet (group 8). Note epithelial hypertrophy, absence of stratum granulosum, absence of stratum corneum, and atypical basal cells. H.&E., X 870. *F*. Vitamin A, 5×10^4 i.u./pellet (group 10). Note absence of keratinization, columnar appearance of epithelial cells. H.&E., X 870.

resulting in similar appearance was also frequent in these groups, but could be distinguished from peg-like downgrowths by comparing sections made in one plane with those made by rotating the plane of section 90 degrees; folds "disappeared" at 90 degrees; whereas peg-like downgrowths were evident in both planes. Epithelial downgrowths were composed of undifferentiated, somewhat hyperchromatic epithelial cells, with many mitotic figures, and were surrounded by a basement membrane visible with the PAS technique. In no case was the striated muscle invaded by such downgrowths.

In groups 9 to 11, but most frequently in group 10, a markedly atypical cell type (Fig. 2f) was observed. Pale nuclei, somewhat vesicular and misshapen, were often situated at the base of columnar cells. The cytoplasm was clear and non-staining except at the base of the cell near the nucleus. Such cells were most often located in focal areas of the basal and adjacent epithelial layers; less frequently they were observed in the uppermost epithelial layers but were usually replaced by cells similar in detail but flattened and partly squamous rather than columnar. Coarse cytoplasmic granules suggestive of mucus were demonstrated in some foci of these atypical, columnar cells (Figs. 3c and 3d). These granules were PAS-positive after treatment with various diastase preparations for 30 minutes.

At the highest levels of vitamin A applied, as trochees (group 12), no epithelium was observed on histologic examination (Fig. 3e). Cheekpouch specimens appeared to consist solely of an edematous submucosa, markedly infiltrated by leukocytes and covered by necrotic debris occasionally interspersed with areas of new granulation tissue.

Effect of Vitamin A on Left (Untreated) Pouch. The left (untreated) cheekpouch epithelium was similar in thickness and appearance to control epithelium (left pouch of group 3) at dose levels up to 10^3 i.u. vitamin A/pellet (groups 5 to 7). At higher dose levels, the epithelium appeared thicker than the control epithelium; increased glycogen was present in the intermediate epithelial layers of these groups.

COMMENT

The normal cheekpouch mucosa (Figs. 2a and 3b) consists in part of a typical "soft"-keratinizing epithelium except for the presence of isolated small clusters of cells containing glycogen. Glycogen is generally absent in normal, similar soft-keratinizing epidermis,[3,14] but is present normally in some areas of normal oral epithelium.[25]

Application of a control pellet, with or without the ether-oil vehicle (groups 2, 3), results in a significant thinning of the epi-

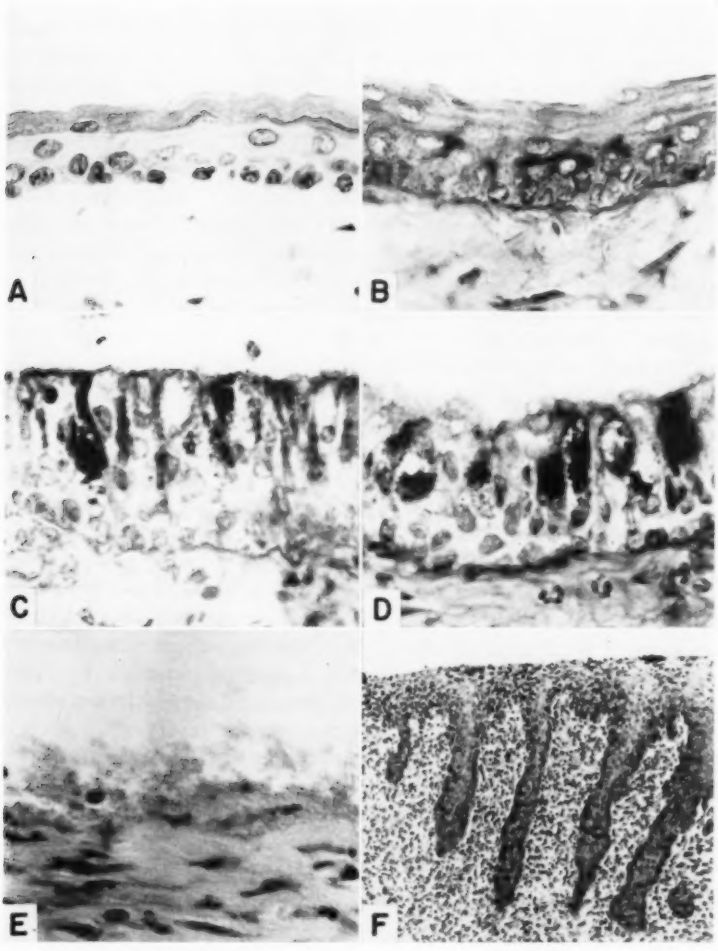

Fig. 3.—*A*. Oleic acid, mole-equivalent of 10^5 i.u. vitamin A/pellet (group 4). Note lack of epithelial hypertrophy and similarity to Figure 2 *B*. H.&E., X 870. *B*. Normal untreated epithelium (group 1). A group of cells containing fine PAS-positive granules which are diastase-digestible glycogen. PAS without diastase, light hematoxylin, X 870. *C*. Vitamin A, 5×10^4 i.u./pellet (group 10). Note coarse PAS-positive granules and, in superficial areas, fine PAS-positive granules and amorphous material. Compare with Figure 3 *D*. PAS without diastase, light hematoxylin, X 870. *D*. Vitamin A, 5×10^4 i.u./pellet (group 10). Diastase treatment has removed glycogen. Coarse PAS-positive, diastase-resistant granules, presumably mucus. PAS after diastase treatment, light hematoxylin, X 870. *E*. Vitamin A, 10^5 i.u./pellet (group 11). Area where epithelium has been replaced by amorphous material overlying subepithelial connective tissue. H.&E., X 870. *F*. Vitamin A, 10^5 i.u./pellet (group 11). Note epithelial downgrowths into subepithelial connective tissue. H.&E., X 160.

thelium. On the basis of flattened (oval) nuclei of the epithelium observed in these groups, such thinning is interpreted as due primarily to mechanical stretching of the epithelium by the pellet. Although thinning may also be due in part to a chemical or physical effect of the pellet base upon epithelial growth or differentiation, the over-all effect is minimum.

Oleic acid, known to promote epithelial hyperplasia, hypertrophy, and damage at massive dose levels in rodent epidermis[13,21] and in preliminary experiments with cheekpouch epithelium, produces no significant effect upon cheekpouch epithelium when applied at a dose level equivalent in moles to the largest amount (10^5 i.u./pellet) of vitamin A employed here in paraffin pellets. The slight increase in thickness of the left pouch after oleic acid treatment of the right pouch is difficult to explain; it may be the result of some systemic effect of the oleic acid uncomplicated by the interference of a paraffin pellet. As previously reported in our study of mouse epidermis,[9] the effect of vitamin A is again not reproduced by comparable amounts of oleic acid, and these results contribute further support to a concept of a more or less "specific action" of vitamin A upon keratinizing epithelia.

Small amounts of vitamin A (groups 5 to 7) applied to the cheekpouch mucosa produce hypertrophy of the epithelium roughly in proportion to the log of the dose, and the stratum granulosum is thickened with an increase in size of individual granules; a stratum corneum is present. On the basis of mitotic studies of mouse epidermis, it seems likely that this thickening is the result of an increase in epithelial cell division (hyperplasia), rather than primarily any specific "anti-keratinizing" effect of the vitamin within this dose range. However, the lack of difference in mean thickness of the stratum corneum between right pouches of vitamin A-treated (groups 5 to 7) and control groups (group 3) suggests a reduced rate of cornification of the hyperplastic vitamin-treated epithelium.

After large amounts of vitamin A, cheekpouch epithelium is still apparently hyperplastic but no longer undergoes keratinization (groups 9 to 12). Thinning or absence of the stratum corneum is accompanied by a similar thinning or absence of the stratum granulosum. Epithelial cells are markedly atypical (Fig. 2e), and glycogen is accumulated in the superficial cell layers; these changes are clearly the effects of a disturbance in normal differentiation (including keratinization). The reduced epithelial response observed at higher dose levels (groups 9 to 12) is interpreted as the result of reduced epithelial

mitotic activity, compared to the marked hyperplasia after moderate levels of vitamin A. The presence of columnar epithelial cells containing PAS-positive, diastase-resistant granules after large amounts of vitamin A (group 10) strongly suggests a mucous metaplasia of the normally soft-keratinizing epithelial cells; it is interesting that this reaction is observed at dose levels higher than that at which hyperplasia is most evident. It is suggested that such mucous metaplasia may tend to occur at even lower dose levels but be masked where hyperplasia is marked.

At the highest level of vitamin A employed, the epithelium is completely absent and there is marked damage to the submucosa. This effect is interpreted as a complete inhibition of epithelial mitotic activity and of regeneration after the toxic destruction of the original epithelium. However, some part of this response may be due to the trochee vehicle in group 12, since a control vehicle was not available for testing; nevertheless, occasional similar ulceration was present in group 11.

Accordingly, with increasing amounts of vitamin A, the following sequence of responses is obtained in the cheekpouch mucosa: a) increased mitotic activity, at low dose levels; b) absent keratinization with less marked hyperplasia, at intermediate dose levels; c) mucous metaplasia following a complete block of normal differentiation, together with an inhibition of the hyperplasia observed at lower dose levels; and d) epithelial cell death with suppressed regeneration, at massive dose levels.

Hypertrophy of the left (untreated) pouch after large amounts of vitamin A (groups 8, 9) is interpreted as a systemic effect of the vitamin similar to that reported in studies of rat epidermis[23] after large oral doses of vitamin A.

In the mouse, large amounts of locally-applied vitamin A[9] produce epidermal hyperplasia complicated by the differential responses of epidermal adnexae (e.g., hair follicles); the resulting effects are often difficult to interpret, and the epidermis varies in thickness with different stages of the hair cycle.[4] The simple epithelium of the golden hamster cheekpouch, with the absence in this species of epidermal adnexae and of rete pegs, facilitates interpretation of changes in proliferation and differentiation and should prove to be a useful tissue for future experimental studies. In the mouse, the largest amounts of vitamin A applied percutaneously produce death of the animal. Although occasional foci of intracellular

accumulation of PAS-positive, diastase-resistant amorphous material were observed in mouse epidermis after massive amounts of vitamin A, such changes occurred together with marked changes in adnexal structures and in mice severely toxic from systemic effects of the vitamin. The present cheekpouch findings represent the first report of possible mucous metaplasia *in situ* resulting from vitamin A treatment.

In conclusion, the effects of vitamin A applied locally to the hamster cheekpouch vary considerably with increasing dose level of the vitamin from hyperplasia through inhibition of both keratinization and hyperplasia to mucous metaplasia and, eventually, to cell death and suppressed epithelial regeneration.

SUMMARY

1. The effects of local application of vitamin A in paraffin pellets to hamster cheekpouch epithelium were studied, and compared with the effects of a comparable amount of oleic acid.

2. Treatment for ten days with a single pellet containing 10^2 - 10^3 i.u. vitamin A produced epithelial thickening, an apparent increase in epithelial mitotic activity, a thickened stratum granulosum, and a striking increase in size of keratohyalin granules. Epithelial thickening was roughly proportional to the log of the dose.

3. With increasing amounts of vitamin A above the levels of 10^3 i.u./pellet, an increasing interference with the keratinization process and a decreasing degree of epithelial hypertrophy occurred. At the level of 10^5 i.u./pellet, the remaining epithelium was no thicker than the control epithelium, exhibited neither keratin nor stratum granulosum, and appeared stratified cuboidal in type. Epithelial downgrowths were also observed.

4. At the highest level of vitamin employed (1.5×10^5 i. u. trochee), no epithelium was present after ten days.

5. At the level of 5×10^4 i.u./pellet, several areas indicating possible mucous metaplasia were observed.

6. The untreated contralateral pouch of vitamin A-treated hamsters showed a suggestion of epithelial hypertrophy at higher dose levels, but such thickening was not statistically significant in all high-level groups.

7. Oleic acid, in the amount equivalent in moles to 10^5 i.u. vitamin A/pellet, had no significant effect on cheekpouch epithelium.

8. The effects of topical vitamin A treatment of the normally keratinizing epithelium of the hamster cheekpouch range from hyperplasia at low dose levels, to inhibition of keratinization at intermediate dose levels, to mucous metaplasia at high dose levels, and to epithelial cell death with suppression of proliferation (absence of regeneration) at massive dose levels.

CANCER RESEARCH GENETICS LABORATORY
UNIVERSITY OF CALIFORNIA, BERKELEY

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REFERENCES

1. Bern, H. A.: Histology and Chemistry of Keratin Formation. Nature 174: 509-511, 1954.

2. Bern, H. A., Elias, J. J., Pickett, P. B., Powers, T. R., and Harkness, M. N.: The Influence of Vitamin A on the Epidermis. Am. J. Anat. 96:419-448, 1955.

3. Bradfield, J. R. G.: Glycogen of Vertebrate Epidermis. Nature 167:40-42, 1951.

4. Chase, H. B., Montagna, W., and Malone, J. D.: Changes in the Skin in Relation to the Hair Growth Cycle. Anat. Rec. 116:75-92, 1953.

5. Fell, H. B., and Mellanby, E.: Metaplasia Produced in Cultures of Chick Ectoderm by High Vitamin A. J. Physiol. 119:470-488, 1953.

6. Fisher, L., and Hermann, F.: Some Effects of Topical Viatmin A Upon Human Epidermis. Arch. Dermatol. 75:667-670, 1957.

7. Gillette, R.: Normal Growth and Development of Hamster Pouch Epithelium. Anat. Rec. 128:555-556, 1957.

8. Hopper, A. F., and Mathews, W. W.: Metaplasia and Other Phenomena in Some Intraocular Transplants of Adult Mouse Epithelia. Anat. Rec. 117:629, 1953.

9. Lawrence, D. J., and Bern, H. A.: On the Specifiicity of the Response of Mouse Epidermis to Vitamin A. J. Invest. Dermatol. 31:313-325, 1958.

10. Leblond, C. P.: Histologic Structure of Hair, with a Brief Comparison to Other Epidermal Appendages and Epidermis Itself. Ann. N. Y. Acad. Sci. 53:464-475, 1951.

11. Lever, W. F.: Histopathology of the Skin. 2nd Ed., J. B. Lippincott Co., Philadelphia, pp. 328-329, 1954.

12. Lutz, B. R., Fulton, G. P., Patt, D. I., Handler, A. H., and Stevens, D. F.: The Cheek Pouch of the Hambster as a Site for the Transplantation of a Methylcholanthrene-Induced Sarcoma. Cancer Res. 11:64-66, 1951.

13. Montagna, W.: Penetration and Local Effect of Vitamin A on the Skin of the Guinea Pig. Proc. Soc. Exper. Biol. Med. 86:668-672, 1954.

14. Montagna, W.: Structure and Function of the Skin. New York, Academic Press, 1956.

15. Mulay, D. N., and Urbach, F.: Local Therapy of Oral Leukoplakia with Vitamin A. Arch. Dermatol. 78:637-638, 1958.

16. Priddy, R. E., and Brodie, A. F.: Facial Musculature, Nerves and Blood Vessels of the Hamster in Relation to the Cheek Pouch. J. Morphol. 83:149-180, 1948.

17. Rowe, N. H., and Gorlin, R. J.: The Effect of Vitamin A Deficiency Upon Experimental Oral Carcinogenesis. J. Dental Res. 38:72-83, 1959.

18. Salley, J. J.: Experimental Carcinogenesis in the Cheek Pouch of the Syrian Hamster. J. Dental Res. 33:253-262, 1954.

19. Salley, J. J.: Histologic Changes in the Hamster Cheek Pouch During Early Hydrocarbon Carcinogenesis. J. Dental Res. 36:48-55, 1957.

20. Salley, J. J., and Bryson, W. F.: Vitamin A Deficiency in the Hamster. J. Dental Res. 36:935-944, 1957.

21. Schaff, V. F., and Gross, F.: Tierexperimentelle Untersuchungen mit Salben und Salbengrundlagen. Dermatologica 106:357-378, 1953.

22. Sherman, B. S.: The Effect of Vitamin A on Epithelial Mitosis *in Vitro*. Anat. Rec. 133:429, 1959.

23. Studer, A., and Frey, J. R.: Über Hautveränderungen der Ratte nach grossen oralen Dosen von Vitamin A. Schweiz. Med. Woch. 17:382-384, 1949.

24. Szabo, G.: Effect of Vitamin A on Human Skin *in Vitro*. Excerpta Medica, Section 1, 13:211, 1959.

25. Weinmann, J. P., and Meyer, J.: Types of Keratinization in the Human Gingiva. J. Invest. Dermatol. 32:87-94, 1959.

26. Weiss, P., and James, R.: Vitamin A and Skin Keratinization *in Vitro*: Experimental Dissociation of Induction and Realization Phases in Cytodifferentiation. Science 119:587, 1954.

27. Welsh, A. L.: Differential Diagnosis of Leukoplakia, Leukokeratosis and Cancer in the Mouth. C. C. Thomas, Springfield, 1955.

LI

SOME ASPECTS OF THE BIOCHEMISTRY OF ACOUSTIC TRAUMA

YASUSHI KOIDE, M.D. MAKOTO YOSHIDA, M.D.
MASARU KONNO, M.D. YUICHI NAKANO, M.D.
YOSHIE YOSHIKAWA, M.D. MASAO NAGABA, M.D.
AND MASANORI MORIMOTO, M.D.
NIIGATA-SHI, JAPAN

That loud sound has a deleterious action upon the cochlea has been well documented in both human and experimental animals since the time of Wittmaack and Yoshii. Such injuries may develop as a result of exposure to sustained sounds of high intensity, such as machinery noise. An equally severe injury may be caused by a shock wave created by an explosion.

Most of the early works, reviewed by Kemp,[1] on what we now call acoustic trauma, consist of investigation with animals and was a study of histologic changes in the inner ear. This has given information about the noise susceptibility and the localization of the changes. For more than fifteen years it has been possible to study the functional capacity of the ear, using the method of recording the cochlear microphonics, under different acoustic conditions. This study has opened a new field of research, explaining many complicated physiologic and pathologic procedures. However, the research in this field has contributed only little to the knowledge about the changes of metabolic process in the inner ear under different experimental conditions.

The most early development[2,3] in this field has been the identity of the nucleic acids in individual nerve cells in the spiral ganglion and the evaluation of vulnerability of nucleic acid metabolism under different acoustic conditions.

Since the early observation, many attempts have been made to evaluate the biochemical changes in the inner ear. Today it appears

From the Department of Otolaryngology, Niigata University School of Medicine, Niigata, Japan.

to be established beyond reasonable doubt that after exposing animals to either noise or shock waves the demonstrable decrease in the nucleic acid and protein concentration in the cytoplasm is observed in the spiral ganglion cells,[4-8] outer hair cells[8] and stria vascularis.[8]

In a study of the influence of noise on the inner ear Bejdl and Krejci[9] have employed radioactive phosphorus, P^{32}. In their experiment the turn-over rate of P^{32} for the organ of Corti and spiral ganglion cells was slower under acoustic conditions. A number of reports have appeared, accounting for the effects of acoustic stimulation upon the inner ear, with a marked inhibitory effect on amino acid[10,11] and protein[2-5,12] metabolism.

The biochemical changes caused by acoustic stimulation have been also evaluated in the auditory center. According to Mizukoshi[13] and Uno,[14] the changes in the auditory center of animals exposed to weaker sound consist of increase in nucleic acid concentration and turn-over rate of P^{32}, while by higher intensity the nucleic acid concentration decreases.

On the basis of Nachmansohn's hypothesis supporting the involvement of acetylcholine in the chemical mediation in the nerve, attempt in this direction was made. Martini[15] claimed that acetylcholine can be demonstrated in the perilymph on stimulation of the inner ear. However, Gisselsson[16] tried to check his results by carrying out similar experiments but was unable to observe any acetylcholine.

The chemical energy is produced by the combustion of foodstuffs in living matter and then is transformed into a special kind of chemical energy before it is utilized for other types of metabolism, e.g., protein, amino acid, nucleic acid and phosphorus metabolism.

A review of former experiments cited above shows that loud sound caused many types of biochemical changes within the inner ear. This feature suggests a continuity between different types of metabolic alteration caused by loud sound and thus leads to a unifying concept; many types of metabolic alteration which appear totally different are in fact modification of alteration of the basic system (namely, the energy-producing system), by which the terminal pathways of metabolism are maintained. Of the many steps of energy-producing process, the author[17] has assumed that oxygen acts as a limiting factor in the maintenance of its steady state within the inner ear.

Thus it is reasonable to suppose that, in the initial step of onset of acoustic trauma, the most pronounced biochemical change in the

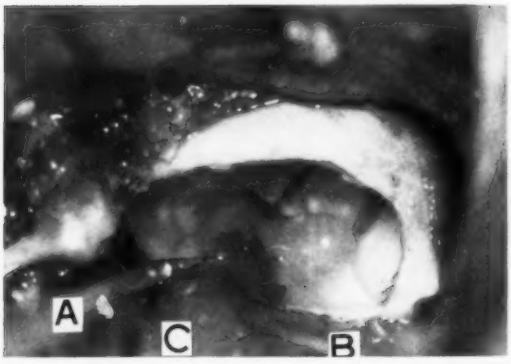

Fig. 1.—The measurement of oxygen tension in the cochlea of a guinea pig. A - platinum microelectrode; B - Ag-AgCl electrode; C - cellulose pulp.

inner ear is the disturbance of the energy-producing system which may be produced by oxygen deprivation or by mechanical disruption of the respiratory chain in the mitochondria.

According to Vosteen,[18] after exposure of animals to loud sound, succinic dehydrogenase has disappeared in the organ of Corti, and oxygen deprivation has accelerated this histochemical change. Recently, Misrahy et al.[19] and Koide et al.[20] have found that the oxygen tension in the inner ear has decreased upon the exposure to loud sound. These observations support the authors' hypothesis.

The original purpose of the present investigation is to demonstrate whether or not any change in energy-producing system arises in the inner ear upon exposure to loud sound and shock waves. As such changes have been found, the experiments have been designed to investigate the detailed pattern of changes and to suggest the locus of acoustic trauma.

EFFECTS OF EXPOSURE TO LOUD SOUND AND SHOCK WAVES UPON THE OXYGEN TENSION

Method of Recording the Oxygen Tension in the Labyrinth. The method of recording the oxygen tension in the labyrinth has been already described.[21] However, the modified method was used in the present experiment.

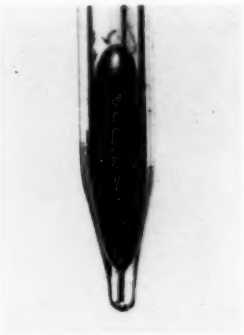

Fig. 2.—Platinum electrode. This electrode was prepared by fusing a platinum wire, 200 μ diameter, into a soft-glass tube.

Each animal, rabbit and guinea pig used, was deeply anesthetized with an appropriate intraperitoneal dosage of a solution of Isozol (5-allyl-5[1-methyl-butyl]-2-thiobarbiturate), supplemented with curare, and artificial respiration was used throughout the experiments.

Incision was made through the skin in the mandibular region and the bulla was exposed. The surface of the bulla was then cleaned and, with a dental drill, an opening was made to expose the cochlea.

The tip of platinum microelectrode, described already in the former report,[21] was introduced into various parts of the cochlea through a small hole made with a microdrill. Then a small piece of cellulose pulp moistened with physiological saline was placed around the tip of platinum microelectrode, and the reference electrode was placed in the cellulose pulp.

Method of Recording the Oxygen Tension in the Brain Cortex of the Temporal Area. Rabbits were used for the experiments. Incision was made through the skin in the supra-auricular region and the temporal bone was exposed.

The tip of the platinum electrode, shown in Figure 2, was placed on the surface of the brain cortex of the temporal area through a small hole with a dental drill. Care was taken to avoid any injury in the blood vessels of the brain cortex while making the hole and placing the electrode. Then small pieces of cellulose pulp described above were

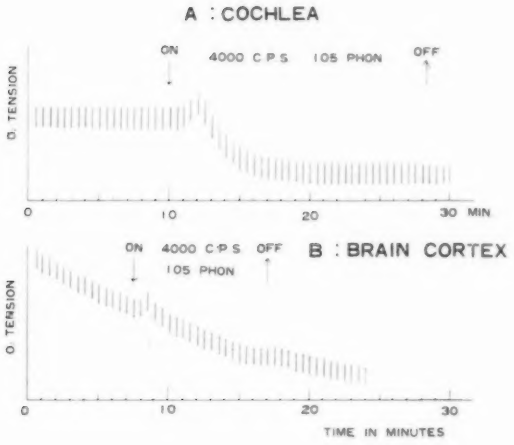

Fig. 3.—The effects of loud sound on the oxygen tension in the scala tympani of the rabbit cochlea and in the brain cortex of a rabbit. When the platinum electrode was placed on the brain cortex, there was, as usual, a spontaneous downward deflection of oxigraphic trace. Thus, the effect of sound stimulation was represented by the transitional changes in the trace.

placed around the tip of the platinum electrode and the reference electrode was placed in the cellulose pulp.

Pure Tone Stimulation. A loudspeaker was employed as sound source. The animals were placed at a distance of 5 cm, and the sound was delivered to the animals. The sound pressure level was measured by a dynamic microphone placed at a distance of 5 cm from the loudspeaker.

Application of Shock Waves. At a distance of 10 cm, the animals were exposed to shock waves which were produced by detonation of explosives. The explosives which are called "cracker" in our country, are commercially available. Oscillograph recording of detonation has shown that the positive duration was approximately 100 msec and the maximum intensity of noise was 100 phon at a distance of 2 m.

Experimental Results. Data gathered on animals indicate that the oxygen tension in both the inner ear and the brain cortex is affected by sound exposures.

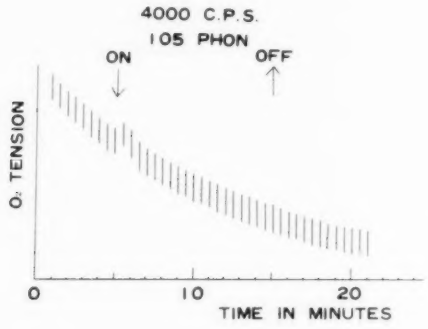

Fig. 4.—The effect of loud sound on the oxygen tension in the scala tympani of the damaged cochlea of a rabbit.

Referring to Figure 3 it can be seen that at a higher sound level, even though the oxygen tension in both the inner ear and the brain cortex increases initially, the oxygen tension immediately begins to drop off. The next experiment was carried out to see if there would be any change in the oxygen tension for lower-level test tone of 60 phon as demonstrated in Figure 3 for higher-level test tone of 105 phon. But there were no changes in the oxygen tension.

By introducing a needle into the membranous cochlea of the basal turn so as to produce damage to the inner ear, the decrease in the oxygen tension in the inner ear shown in Figure 4 was produced. Here by the exposure to sound stimuli there was no change in the oxygen tension, except for a brief rise immediately after stimulation.

Presented in Figure 5 are data on changes in the oxygen tension in the inner ear of a rabbit that breathed two prepared gas mixtures of oxygen and nitrogen (oxygen at 10, and 5 per cent by volume). Comparison was made between the changes of oxygen tension in the acoustically stimulated animal and in the animal in want of oxygen. Then it was observed that the decrease in the oxygen tension in the inner ear during sound stimulation was more severe than the decrease in the oxygen tension caused by breathing the 5 per cent mixture.

According to Beck and Beickert,[22] histologic changes occurred in the inner ear during a 30-minute period of deprivation on the 5 per cent mixture. Gulick[23] has shown that, on the animal deprived of oxy-

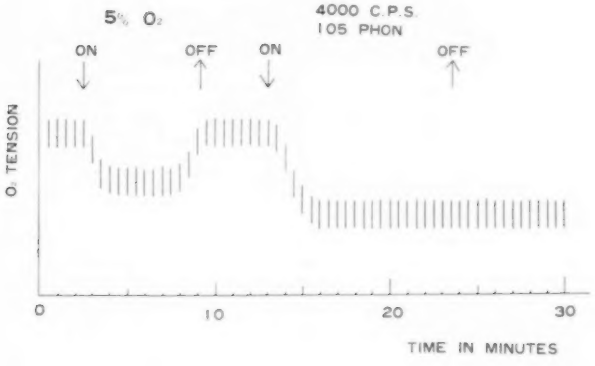

Fig. 5.—The effects of oxygen deprivation and loud sound on the oxygen tension in the scala vestibuli of the guinea pig cochlea.

gen by breathing the 5 per cent mixture, the rapid drop was observed in the cochlear microphonics and partial recovery occurred rapidly after the restoration of air, but total recovery was not observed even though hemoglobin saturation was high as it had been prior to deprivation. These investigations show that irreversible changes appear in the inner ear after severe oxygen deprivation.

Thus, it is suggested that the decrease in the oxygen tension in the inner ear caused by sound stimulation is one of the important factors in bringing on the onset of acoustic trauma.

As shown in Figure 6, upon exposures to shock waves, a different pattern exists regarding changes in the oxygen tension in both the inner ear and brain cortex of the temporal area. The exposures of animals to shock waves failed to produce any observable change in the oxygen tension, except for a brief rise of the oxygen tension in the inner ear immediately after exposure to shock waves. However, the brief rise was not observable after repeated exposures of the animal to shock waves.

There is an interesting experimental fact associated with the nonresponse state which occurred after repeated exposure to shock waves. The oxygen tension in the intact inner ear begins to increase, as

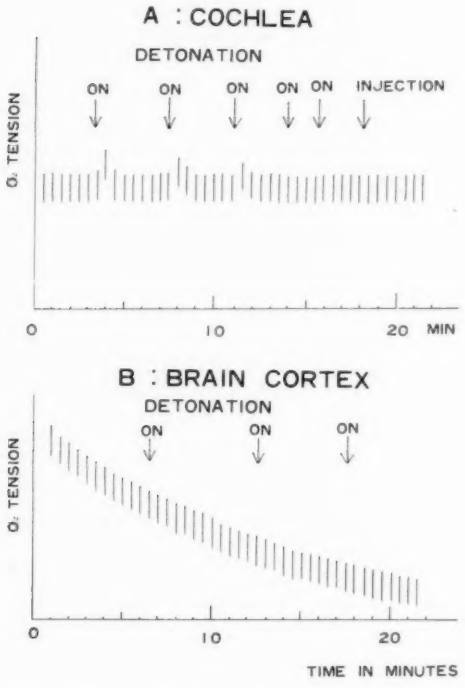

Fig. 6.—The effects of detonation on the oxygen tension in the scala tympani of the guinea pig cochlea and in the brain cortex of a rabbit. One mg of sodium nicotinate was injected intraperitoneally after repeated detonations, and had no effect.

nicotinate is administrated intraperitoneally (Fig. 7), but the effect of nicotinate cannot be produced in the above non-response state.

EFFECT OF EXPOSURE TO LOWER-LEVEL TEST TONE UPON GLUCOSE CONCENTRATION IN THE PERILYMPH WITH REFERENCE TO THE LABYRINTHINE BLOOD FLOW

In the previous section, it was stated that one of the effects of a higher-level test tone on the inner ear is a decrease in the oxygen tension in the inner ear under test. However, there was no change in the oxygen tension during exposure, 30 minutes or less, to a lower-level test tone. Thus the next experiment was carried out to see if

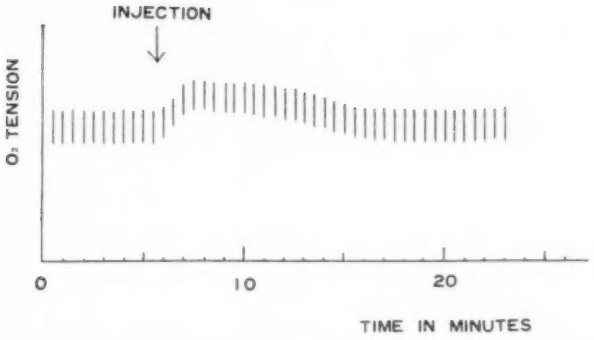

Fig. 7.—The effect of nicotinic acid on the oxygen tension in the scala vestibuli of the guinea pig cochlea. One mg of sodium nicotinate was injected intraperitoneally.

there would be any metabolic change in the inner ear during long lasting exposure to lower-level test tone. In order to study this problem, perilymph from the rabbit was analyzed for glucose.

Application of Noise Stimuli. Stimuli were restricted to white-noise produced by means of an audiometer. The output from the audiometer was fed into a power amplifier which drove the loudspeaker. Aerial sound was conducted into the left ear by a tube leading from the speaker. A cannula on the end of the tube was inserted into the external auditory meatus and tied securely. An ear-plug was tightly inserted into the right ear, which maintained intact as control, so as to obstruct the external auditory meatus completely. The sound pressure level was measured by a dynamic microphone placed at the tip of the cannula. Each experimental animal was isolated in a soundproof room and exposed to sound stimuli (60 phon' 7 hours per day) for one week.

Collection of Perilymph and Chemical Analysis. At the end of exposure to sound stimuli, perilymph was collected under Isozol anesthesia.

An incision was made through the bone of the skull before the auditory meatus, and the bulla was opened with a small curet and as much of the bone removed as is necessary to provide a good view of the oval window. The incus and malleus were removed with the

TABLE I

CHANGES IN THE GLUCOSE CONTENT OF PERILYMPH CAUSED BY NOISE STIMULI

ANIMAL	GLUCOSE CONTENT OF PERILYMPH (mg/dl)	
	RIGHT EAR	LEFT EAR
No. 1	131	141
No. 2	62	160
No. 3	125	138
No. 4	125	125
No. 5	103	119

aid of the binocular microscope. Then the middle ear could be easily exposed and direct visualization of the oval window was possible.

The perilymph of both ears was collected by piercing the oval window membrane with a dry glass capillary carried on a micromanipulator. The glass capillary was made of 2 mm tubing drawn down to 0.3 mm, 1 cm from the tip, and 0.1 mm at the tip.

Although care was taken to avoid the capillaries of the oval window membrane and membranous labyrinth, this was not always possible. If more than a trace of blood was visible, the samples were discarded. The samples obtained ranged from 3 to 7 µl.

The principles of the glucose determination have been published by Kingsley and Reinhold,[24] but the method has been revised by the author[25] to provide increased sensitivity. Because of the limited amount of fluid available, micro-method had to be developed or adapted specially for the purpose. The reader is referred to these publications for details of principles, pipeting, mixing, performing colorimetry, etc., on micro and submicro scale.

Experimental Results. Chemical analysis for glucose has been carried out immediately after the perilymph was collected. The results to be described were obtained with a final series of five animals, in each of which the total procedure was complete without technical fault.

The glucose contents of perilymph were higher in the left ear than in the right ear in control (Table I). This chemical finding

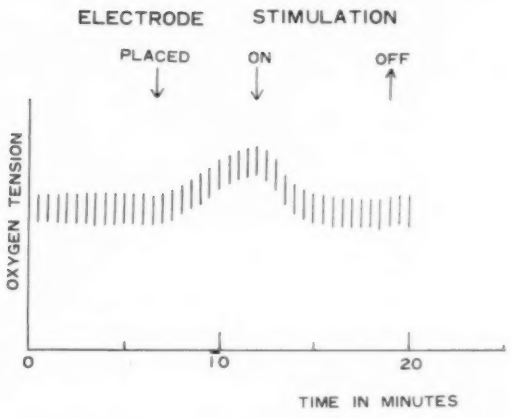

Fig. 8.—The effect of electrical stimulation of the cervical sympathetic trunk upon the oxygen tension in the vestibular perilymph of a rabbit.

agrees with those of Koide,[17] for the rabbits, in regard to the effects of acute and subacute reduction of the labyrinthine blood flow upon the glucose content of perilymph.

Thus the present chemical findings are probably suggestive that a disturbance of the labyrinthine blood flow was produced by the noise exposure and the disturbance was a probable cause of the increase in the glucose content of perilymph.

The possible participation of the labyrinthine blood flow in the regulation of the glucose content of perilymph might be approached from other angles. It is well known that the sympathetic nerve supply does exercise some measures of control upon the cochlea. The effects of sympathetic stimulation were observed by several investigators[26-28] to be a reduction in the cochlear microphonic potentials. Maruyama[29] noted in cats a reduction in the calibre of the labyrinthine artery and a resultant reduction in the cochlear microphonic potentials when the stellate ganglion was stimulated. However, Krejci and Bornschein[30] noted that experiments on cats furnished no evidence for the supposition that the cochlear microphonic potentials are influenced by prolonged sympathetic stimulation.

According to Akiyama,[31] Hojo,[32] Passe,[33] Strong,[34] and Ballenger,[35] blocking the stellate ganglion by procaine or surgical section

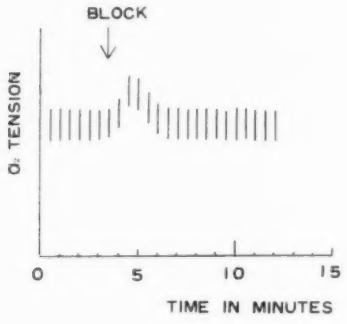

Fig. 9.—The effect of stellate ganglion block on the oxygen tension in the vestibular perilymph of a rabbit.

caused an increase in the calibre of the blood vessels of the inner ear. Maruyama[29] noted in cats an increase in the caliber of the labyrinthine artery and a resultant increase in the cochlear microphonic potentials when the stellate ganglion was blocked. However, Beickert and associates[28] have reported that after blocking the stellate ganglion there was a reduction in the cochlear microphonic potentials.

After reviewing the literature, it is supposed that both stimulating and blocking the stellate ganglion may produce a change in the oxygen tension in the inner ear, accompanied by a change in the glucose content of perilymph. The following studies were undertaken in an effort to explore these problems.

The experiments were performed on rabbits anesthetized with Isozol, supplemented with curare, and artificial respiration was used. The cochlea on the side to be investigated was then carefully exposed by the lateral approach. The oxygen tension was recorded in the ampulla of the lateral semicircular canal by the platinum microelectrode. The reference electrode was placed on the cellulose pulp described above, which was placed around the tip of the platinum electrode.

The cervical sympathetic trunk was laid free in the usual manner. In order to attain as nearly physiological conditions as possible, the absolute minimum amount of retraction was used, particular care being taken to avoid pressure on the carotid vessels, pharyngeal wall

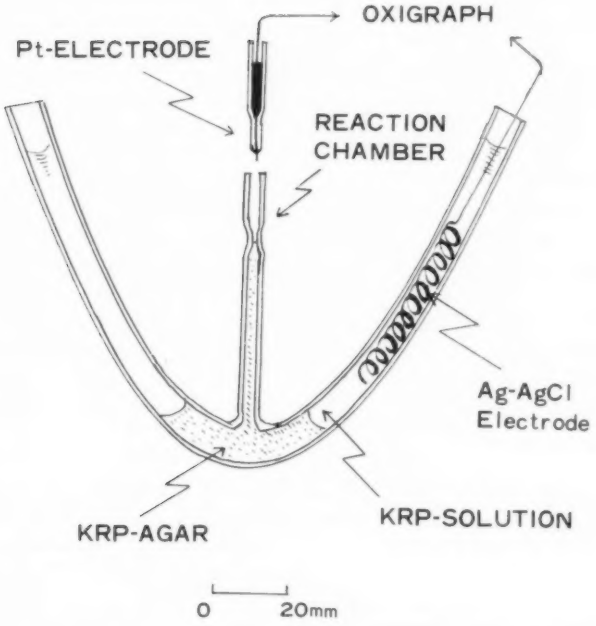

Fig. 10.—The reaction vessel for oxigraphic measurement of tissue respiration. The reaction chamber is made from glass-tubing 3 mm in internal diameter, and filled with substrate solution. The tissue to be examined is placed in the chamber. Then, inserted at the tip of the chamber is a platinum electrode with a tapered tip which extends into the chamber. The most accurate data regarding tissue respiration are obtained, when the platinum electrode is rotated gently by hand.

and the nerve trunks. The electrical stimuli were delivered by a square wave generator. Their frequency was 60 stimuli p.s.

Block of the stellate ganglion was performed using one per cent procaine without adrenaline, one ml of solution being injected on the side to be investigated.

Almost immediately after the stimulating probe, which consists of two fine copper wire, was placed on the sympathetic trunk, the oxygen tension was observed to undergo an appreciable increase in size. On sympathetic stimulation, the oxygen tension underwent a rapid diminution in size (Fig. 8). As shown in Figure 9, after

blocking the stellate ganglion there was a distinct increase in the oxygen tension. However, the oxygen tension regained its initial level after several minutes.

Further the effects of both stimulating and blocking the cervical sympathetic trunk upon the glucose content of perilymph were examined. The experiments were performed on rabbits, anesthetized with Isozol. The cochleas of both ears were exposed by the lateral approach, and besides, the left cervical sympathetic trunk was laid free in the usual manner. In each animal, venous blood was collected from the vessels in the preauricular region, followed by collection of perilymph of the right ear through the already exposed oval window, immediately before the stimulation or block was taken. Ten minutes after the stimulation or block was taken, the perilymph of the left ear and the venous blood were collected. All these samples were analyzed for glucose.

TABLE II

EFFECTS OF SYMPATHETIC STIMULATION AND BLOCK UPON THE GLUCOSE CONTENT OF PERILYMPH AND BLOOD

SAMPLE		GLUCOSE CONTENT (mg/dl) STIMULATION			BLOCK		
Perilymph	Left Ear (Before Operation)	100	122	91	100	103	113
	Right Ear (After Operation)	125	138	127	94	95	144
	After/Before Ratio	1.25	1.13	1.39	0.94	0.92	1.27
Blood	Before Operation	125	142	136	130	105	155
	After Operation	147	138	160	150	130	175
	After/Before Ratio	1.17	0.97	1.17	1.15	1.23	1.13

These results are shown in Table II. It has been suggested that the inner ear distinctly underwent increase in the glucose content of perilymph after the sympathetic stimulation. In each animal, the ratio (after/before) of the glucose content of perilymph, which was analyzed before and after sympathetic stimulation, was higher than that of the blood sugar. However, there were no significant changes in the glucose content of perilymph after blocking the stellate ganglion.

Judging from the above facts concerning chemical changes in perilymph caused by a reduction in the labyrinthine blood flow, it

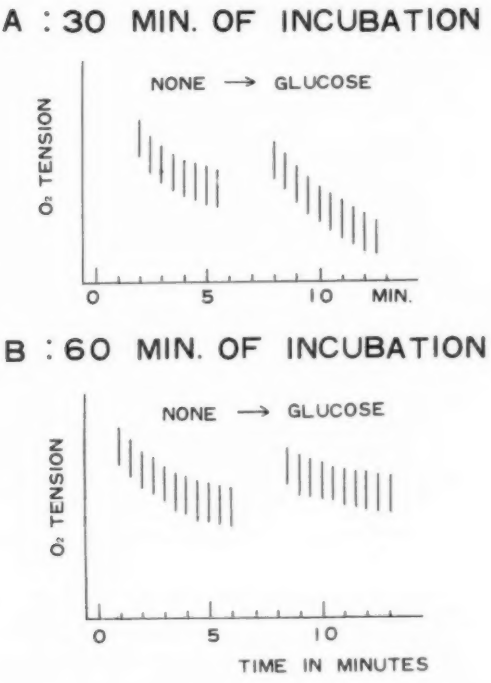

Fig. 11.—The instability of glucose oxidation of the cochlear tissues during anaerobic incubation. Glucose: 10 mM.

seems as if increase in the glucose content reflects hypoxia in the inner ear and improvement of the blood supply of the inner ear as seen after block of the stellate ganglion, but does not lead, on the other hand, to a change in the glucose content. From the physiological point of view, it seems strange that vasoconstriction only should have such an effect. Because both blood and cerebrospinal fluid have higher glucose content than perilymph,[17] any reduction in the blood flow of the inner ear would probably decrease the glucose content to some lower values and, on the other hand, any improvement in the blood supply would increase it to some higher values.

There can be a question that the manifestation of increased glucose content was most likely due to the reduced blood flow. However, as a result of stimulation of the sympathetic nervous center, Koide

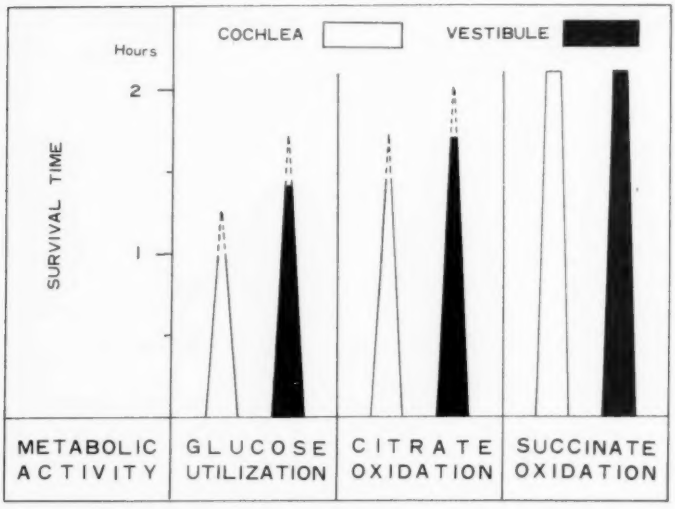

Fig. 12.—The vulnerability of substrate oxidations of the inner ear tissues during anaerobic incubation.

and Nagaba[36] observed, with the rabbits, marked increase in both glucose content of perilymph and oxygen tension in the inner ear. According to Nogi,[37] profound and rapid changes took place in the epithelium of stria vascularis after stimulation of the sympathetic nervous center. But the caliber of the blood vessels remained unchanged. He thinks it likely that the disturbance is reversible, and characterized by the hyperactivity of secretory function. The recent study[38] dealing with stimulation of the autonomic nervous system has revealed that the appearance of diamino acids of slightly higher molecular weight than that of the aliphatic mono-amino acids normally present in perilymph constitutes a good index of sympathetic stimulation.

Although it is not clear what happens to the interior of the inner ear when it shows increase in the glucose content, it seems reasonable to suppose that, as a cause of increase in the glucose content, alteration of the normal capillary permeability of the stria vascularis is of greater importance than change in the caliber of the blood vessels.

That moderate noise stimuli can produce an increase in the glucose content of perilymph has been already described. There can be

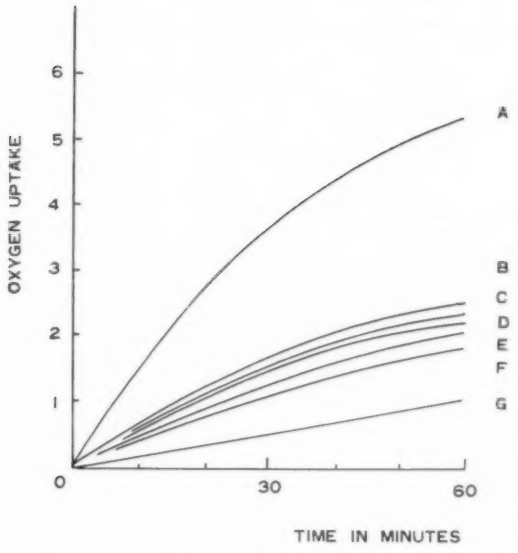

Fig. 13.—Oxidations of substrates in the presence of isolated cochlear tissues (the stria vascularis and spiral ligament) of the guinea pig. Oxygen uptake represents oxygen disappearance measured in μl/mg dry weight of tissue. Substrate, 10 mM; A, succinate; B, glutamate; C, pyruvate; D, malate; E, citrate; F, fumalate; G, none.

no question that in these experiments the manifestation of increase in the glucose content was most likely due to any physiological change in the inner ear following noise exposure since there was no obvious change in the oxygen tension in the inner ear. However, in the present study, the author has no explanation to offer as to why such a change occurred; it is simply suspected that the actual cause should not be hypoxia in the inner ear fluids only.

EFFECTS OF ANOXIA ON THE METABOLIC ACTIVITY OF THE COCHLEAR TISSUES*

The author's experiments have shown that exposure of an animal to high-level test tone produces severe hypoxia in the inner ear, and

* The following abbreviations are used in this section: ATP for adenosine-5-triphosphate; DPN for oxidized diphosphopyridine nucleotide; CoA for conenzyme A; TCA cycles for tricarboxylic acid cycle; KRP solution for Krebs-Ringer-phosphate solution.

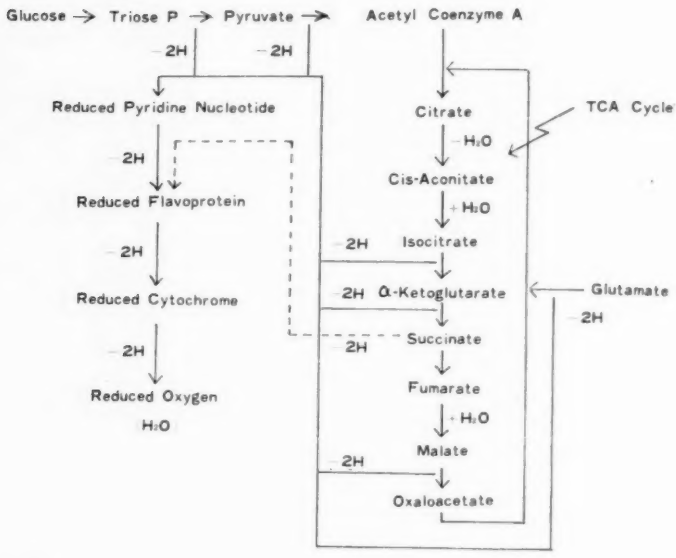

Fig. 14.—Pathways of hydrogen transport from substrate to molecular oxygen. (From Krebs and Kornberg, 1957)

perusal of literature revealed that hypoxia in the inner ear is one of the important factors in bringing on the onset of acoustic trauma. Any interruption of blood flow to the inner ear is one of the main causes of organic disease. Characteristic histological changes follow such vascular occlusion,[39] and it seems likely that these have their origin in chemical and metabolic disturbances produced by oxygen deprivation.

The present communication describes the studies of some of the biochemical events taking place when the supply of oxygen to the inner ear is interrupted. The deficiency is probably the immediate determinants in the dislocation of labyrinthine function following vascular accidents, and thus may be regarded as the primary factor of ischemic damage. The present study is in no sense complete. Several of the more interesting and detailed metabolic pathways were not investigated further. Nevertheless, a general picture of the vulnerability of the energy-producing system in the inner ear tissues has emerged.

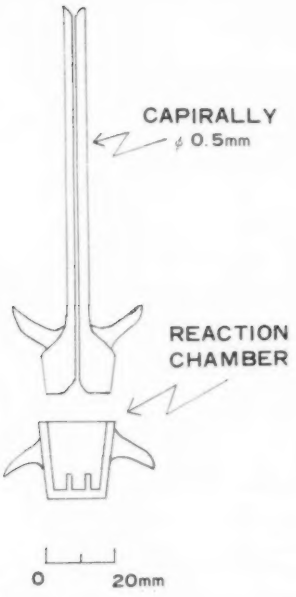

Fig. 15.—The reaction vessel for measurement of glycolytic activity.

The first part of the present experiments was undertaken to ascertain the effects of oxygen lack on the stability of enzymes which oxidize the TCA cycle intermediates and its related substrates. In the second part of this chapter it was reported that the cochlear tissues(the stria vascularis and spiral ligament) lose easily all its glycolytic power if exposed to oxygen lack.

Because the limiting factor[17] of the energy-producing system in the inner ear is oxygen, the main effect of acute arterial obstruction upon the metabolic activity of inner ear tissues may be considered to be primarily a biochemical alteration caused by oxygen lack.

Recently a systematic study of arterial obstruction of the inner ear has been carried out by Kimura and Perlman.[39] However, their blind surgical approach towards the arterial flow to the inner ear made it difficult to carry out a biochemical assay of the inner ear tissues, since a histological examination is needed to ascertain the surgical damage to the inner ear.

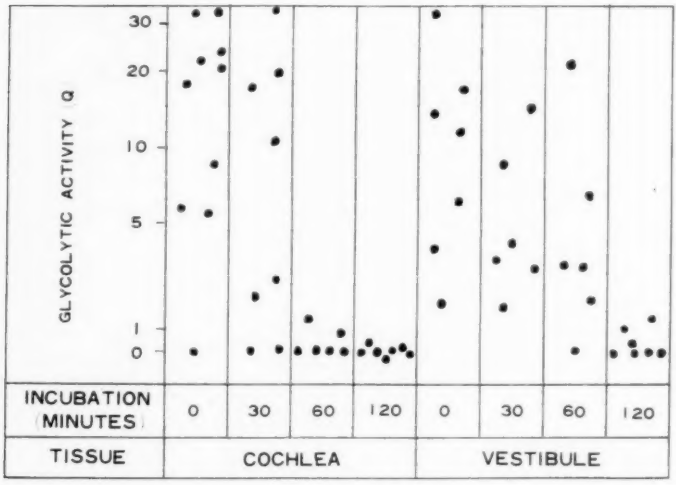

Fig. 16.—The effects of anaerobic incubation on the glycolytic activity in the inner ear tissues. The symbol Q represents glucose utilization measured in μg glucose disappeared/mg dry weight of tissue/hour.

The other surgical approach to the labyrinthine artery has been described by Maruyama.[29] The basal region of the skull was resected perorally, and the dura was cut to expose the labyrinthine artery. Although this procedure gives good visibility on the labyrinthine artery, it resulted in a flow of cerebrospinal fluids from the subarachinoid space. The interruption of blood flow to the inner ear is also achieved by the decapitation of the animal, with simultaneous damage to the VIII nerve and flow of cerebrospinal fluid, and this procedure causes the post-mortem changes in the inner ear tissues.

Each histopathological change which occurs after the vascular interruption described above may be different in some details. However, according to Kimura and Perlman, the early changes following arterial obstruction closely resemble post-mortem degeneration of the inner ear. Then the common factor of interference with oxygen supply to the inner ear may be indicated by all the surgical procedures described above.

The Effects of Oxygen Lack on the Respiration of Inner Ear Tissues. The guinea pigs were killed by decapitation, and then the

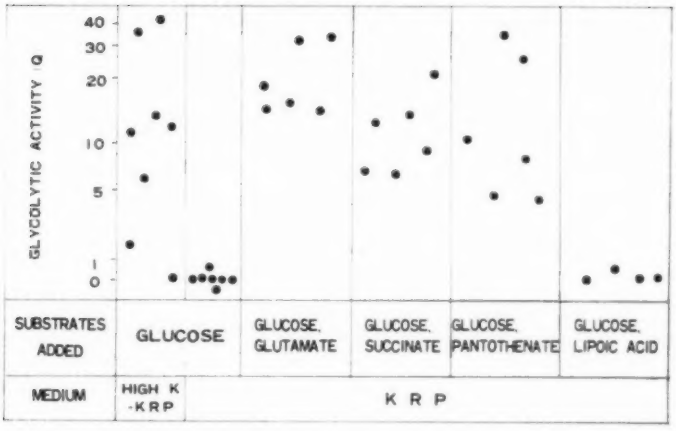

Fig. 17.—Restoration of glycolytic activity in the cochlear tissues (the stria vascularis and spiral ligament) of the guinea pig. Glucose and the other substrates were used in concentration of 10 mm. The modified KRP solution had Na and K values of 13.5 and 148 m equiv. per liter, while the KRP-solution had Na and K values of 154 and 7.0 m equiv. per liter.

whole temporal bones were dissected. They were kept at 37°C. in a thermostat to incubate anaerobically *in vivo* the inner ear tissues. After the anaerobic incubation, the inner ear tissues were taken out with great care in KRP solutions at 0°C. on cracked ice.

The respiration of tissues was observed by means of an oxigraph. The vessel which was modified to increase the sensitivity of measurement is shown in Figure 10. The isolated inner ear tissues were placed in the reaction chamber which was filled with KRP solution.

From the oxigraphic trace it was seen that the addition of cochlear tissues which were already incubated anaerobically *in vivo* for 30 minutes, caused decrease in the oxygen tension in the reaction chamber filled with KRP solution, as indicated by the downward deflection of the trace. When KRP solution was exchanged by KRP solution containing glucose, the oxigraphic trace revealed that the respiration rate of cochlear tissues further increased by exogenous glucose (Fig. 11-A). However, if the tissues were incubated for 60 minutes, the increase in respiration rate by the addition of glucose was not observed (Fig. 11-B).

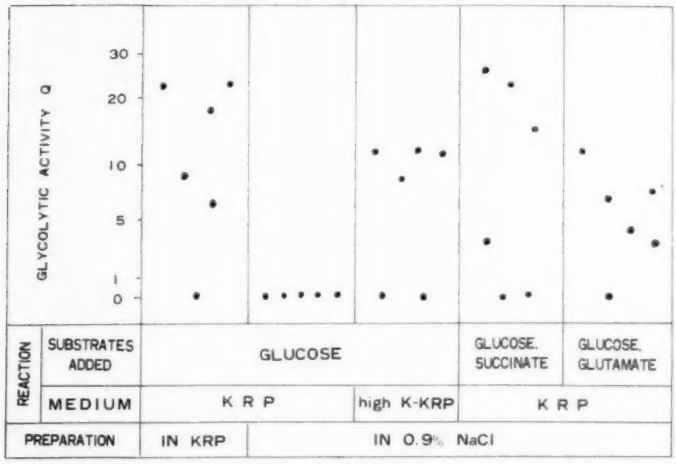

Fig. 18.—Restoration of glycolytic activity in the cochlear tissues (the stria vascularis and spiral ligament) of the guinea pig. Glucose and the other substrates were used in concentration of 15 mM.

The stability of respiration of both cochlear and vestibular tissues was further studied as illustrated in Figure 12. It seems likely that the rate of oxidation of both glucose and citrate, in contrast to the other substrates, declined rather rapidly and that the cochlear tissues were more vulnerable than the vestibular tissues, under anaerobic conditions.

Because the decline of oxidative system in mitochondria is more rapid aerobically than anaerobically,[40,41] the stability of the oxidative system in the inner ear tissues was also examined manometrically by means of an open-tube respirometer (Cunningham-Kirk type[42](under aerobic conditions. After decapitation, the inner ear tissues of a guinea pig were removed rapidly in KRP solutions on cracked ice, and placed in the reaction chamber. After standing at 37°C. for 10 minutes, readings were taken at intervals and the average rate of oxygen uptake was plotted against time at the midpoint of each period. The rapid decline of DPN-linked oxidations occurred during aerobic incubation of the inner ear tissues with a number of the substractes (Fig. 13). However, in the case of succinate, the rate of oxygen uptake did not decline rapidly during the course of the incubation.

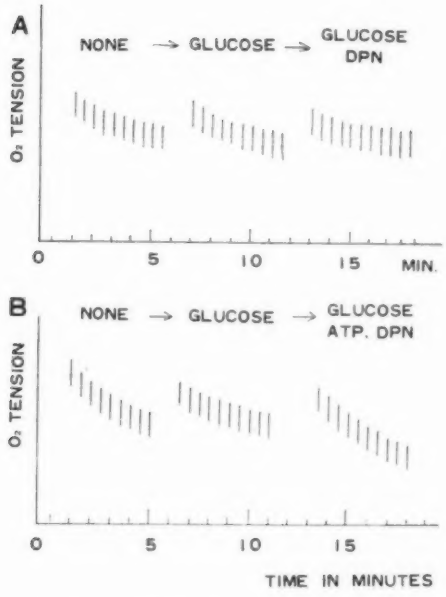

Fig. 19.—Effects of cofactor on respiration of cochlear tissues (the stria vascularis and spiral ligament) of the guinea pig. After decapitation, the cochlear tissues were incubated *in vivo* at 37°C. for 90 minutes, and then removed in KRP solutions on cracked ice. For the experiment the tissues were kept at 37°C., the experimental series in KRP solution + glucose + cofactor, the controls in KRP solution, and in KRP solution + glucose. Glucose, 10 mM; ATP, 50 μM; DPN, 100 μM.

As shown in Figure 14, the oxidations begin in every case with a transfer of hydrogen atoms to a common reagent, DPN. Partial exceptions are fatty acids, succinate, and ascorbic acid. Succinate donate hydrogen atoms directly to flavoprotein, and ascorbic acid reduces directly cytochrome c.[43,44] Then the present data suggests that the site at which the respiration of the inner ear tissues is affected the most remarkably under aerobic and anaerobic conditions is the "DPN-linked" oxidation.

The Effects of Oxygen Lack on the Glucose Utilization of Inner Ear Tissues. The inner ear tissues from guinea pig were suspended in 25 μl of a KRP solution containing 14 mM glucose (pH adjusted to 7.2). The suspension was added to each center well of the reaction

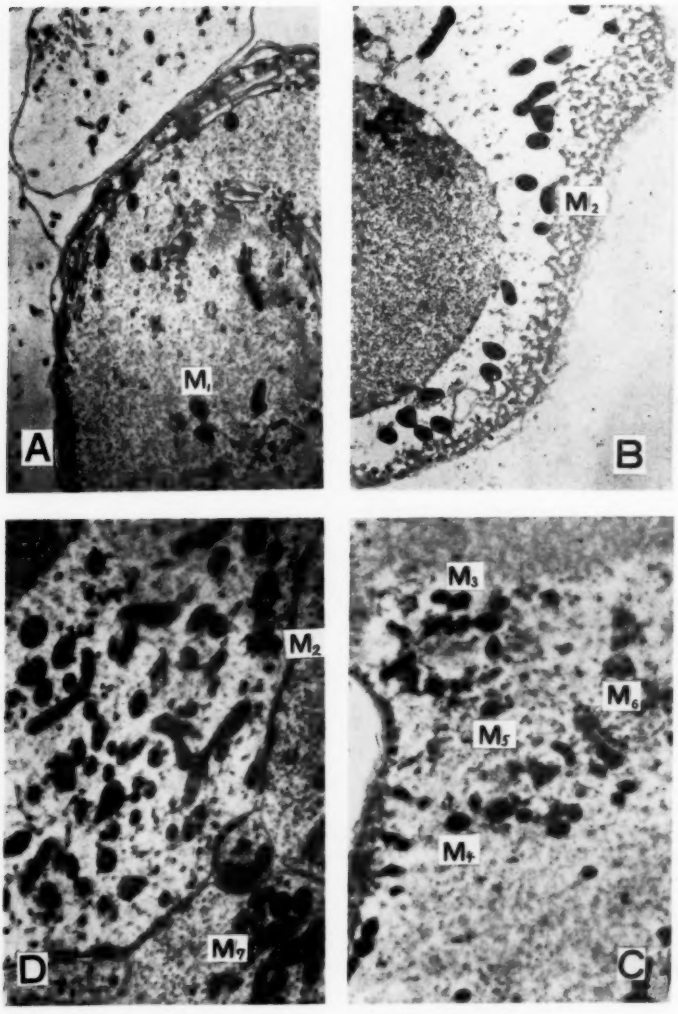

Fig. 20.—Changes in the mitochondria of the outer hair cells of the organ of Corti (guinea pig).

vessel (Fig. 15). Then the reaction vessels were kept at 37°C. in a thermostat. After standings at this temperature for 10 minutes, 5 µl of the substrate solution was collected by a micropipet, and analyzed for glucose. The second value of glucose was taken after one hour. Of course, similar experiment without the tissue had been made as control. At the end of each experiment, weighing of the tissues was carried out by means of a string balance modified from that published by Trevan[45] and Eränkö.[46] Figure 16 shows the effect of oxygen lack on the glucose utilization (Q) of tissues. The cochlear tissues exposed to anaerobic incubation *in vivo* for 30 minutes had only slightly lower glycolytic activity than the tissues prepared immediately after the decapitation. If, however, the cochlea was exposed to anaerobic incubation for a longer period, the activity of tissues decreased considerably, the decrease in activity depending on the oxygen lack. The complete loss of activity resulted from exposing the cochlea to anaerobic incubation for 60 minutes.

On the other hand, the vestibular tissues are highly resistant to anaerobic incubation, and the complete loss of glycolytic activity has not yet been observed during the course of the present study.

The restoration of glycolytic activity, even after 60 minutes of anaerobic incubation, has been observed (Fig. 17). When the impaired tissues of the guinea pig cochlea were suspended in a modified KRP solution (high K, low Na) containing glucose, their glycolytic activity was restored to the normal level. The restoration of glycolytic activity was also found to occur in the impaired tissues which were found to lose all the activity, when the appropriate amount of L-glutamate, succinate, and pantothenate is added to the normal KRP solution.

The loss and restoration of glycolytic activity has also been observed in further experiments (Fig. 18). When the isolated cochlear tissues were washed in isotonic sodium chloride solution, it was found that their glycolytic activity was lost on aerobic conditions in a normal KRP solution containing glucose. Addition of potassium chloride, L-glutamate, and succinate restored the activity. In the experiments on the vestibular tissues, in contrast to that on the cochlear tissues, there was no loss of glycolytic activity.

It is well known[47-52] that potassium leaks out of animal tissue when it is deprived of energy supply and that some substractes, for example, L-glutamate, γ-ketoglutarate, pyruvate, succinate, etc., are required to recover the potassium. Thus the present results favor the

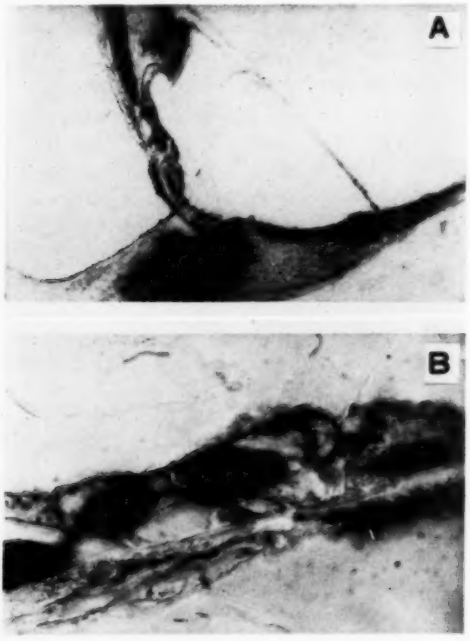

Fig. 21.—Effects of loud sound on the succinic dehydrogenase activity of the guinea pig cochlea. The animal was exposed to loud sound (4000 cps, 105 phon) for 15 hours. As seen in (A) and (B), there exists no significant change in the dehydrogenase activity of the outer hair cells. But, the dehydrogenase activity of the stria vascularis decreased markedly.

view that potassium leaks out of the cochlear tissues during anaerobic incubation in vivo and liberation of potassium ions may be responsible for the loss of glycolytic activity.

The most striking effect of loud sound upon the inner ear is the morphologic change of the cochlea, although there is not any histological confirmation of acoustic vestibular trauma. However, according to McCabe and Lawrence,[53] when the ear of an animal is overstimulated by an intense sound level of 140-150 db, both the vestibule and cochlea are damaged. Although vestibular involvement with loud sound seems not clear enough, it seems reasonable that the vestibule is more resistant to sound stimulation than the cochlea. In the present study, it cannot be concluded that the vulnerability of the inner ear to oxygen

lack and the susceptibility to acoustic stimulation are closely linked together. But it is of interest that the metabolic activity of cochlear tissues is more vulnerable than that of vestibular tissues during oxygen lack, and that loud sound, which accompanies a decrease in oxygen tension in the inner ear, is more injurious to the cochlea than the vestibule.

In recent years, it has been visualized that there exists in tissues a very active mechanism which accomplishes the breakdown of DPN under both aerobic and anaerobic conditions[54-58] and that the loss of DPN in the tissues parallels the decreasing rate of oxygen uptake. On the other hand, it has also been described[40,58] that the loss of bound DPN, being largely referable to enzymic action, results in the decline in the capacity of impaired tissues to carry on glycolysis. According to Lester et al.,[59] DPN is the key enzyme since its omission abolishes the restorative effect of cofactor mixture, and in fact, in some experiments DPN alone was virtually equivalent to the cofactor mixture. It is interesting to notice the fact[60,61] that the addition of DPN and cytochrome c is sufficient to restore respiration even in the case of the γ-keto acids, indicating that the aging did not lead to a loss of CoA, or at least not to a limiting extent.

The experimental facts described in the above references can give the impression that the addition of DPN alone may be essential to restore the oxidative ability, and that DPN is the limiting factor of the decline in tissue respiration. However, in the following experiments, data were shown illustrative of the effect of ATP under conditions where added DPN alone no longer elicits the tissue respiration. Some typical experiments are shown in Figure 19.

In the present experiments, the cochlear tissues were incubated for 90 minutes in the absence of energy supply as described in the former experiments. These conditions are suited for the study of restoration of oxidative ability, since, after the incubation of 90 minutes, the oxidative ability of the tissues is lost almost completely. The two figures represent (A) the damaged tissues tested with DPN alone; (B) with DPN and ATP. As seen, when no glucose oxidation appears, the ability of glucose oxidation could be restored by the addition of ATP and DPN. No effect was obtained with DPN alone.

This data suggest that, when the inner ear tissues are affected by oxygen lack, the limiting factor of metabolic alteration of the tissues is not DPN, but oxidative phosphorylation. Furthermore, according to Krebs and Kornberg,[62] oxidative phosphorylation controls the rate of degradation of substrate.

CHANGES IN THE ORGAN OF CORTI CAUSED BY OXYGEN LACK AND ACOUSTIC STIMULATION

In the former section, it was described that oxygen lack may influence the respiration of the inner ear tissues, especially the DPN-linked respiration, and that oxidative phosphorylation is the limiting factor of biochemical alteration of the inner ear tissues.

Although, in these studies, the biochemical nature of the organ of Corti has not yet been examined, it seems reasonable that no exception to the biochemical rules, described in the former section, may be presented by the organ of Corti. The isolation and analysis of the organ may be helpful in understanding the pathology of acoustic trauma. There exists a wide variety of cell bodies which are distributed in the organ of Corti of completely different histological structure. Therefore, it is impossible to isolate the cell bodies under the examination, and to make measurements of any enzyme.

The significance of the mitochondria in the phenomena of cellular respiration has been accentuated by recent studies[63,64] on integrated enzyme complexes, and precise cytochemical localization has identified the mitochondria as the site of such complexes. The mutual dependence of structural integrity and enzymatic activity indicated that alterations in mitochondria may influence cellular respiration.[65] In the present section, the changes in the external hair cells of the organ of Corti was examined in order to determine the effects of oxygen lack and acoustic stimulation which may affect the mitochondrial structure and the enzymatic properties of the cells.

The material thus far examined for fine mitochondrial structure comes from the guinea pig. The animal was anesthetized with Nembutal and artificial respiration was used. The first group of animals breathed air containing 5 per cent oxygen for 30 minutes. The second group was exposed to shock waves four times, and the third group was exposed to high level test tone for 30 minutes, as described in the former section. The intact animals were used as control.

Immediately after each experiment, the bulla was exposed through the ventral approach, and an opening was made to expose the cochlea. Then, the animal was killed rapidly by incision of the heart, and simultaneously, the cochlea was cut off with a single blow of a small chisel. Within a few seconds after the death, the cochlea was fixed with OsO_4, and then embedded, sectioned, and examined in the electron microscope.

Figure 20 represents the group of mitochondrial profile in the outer hair cells of the organ of Corti. The four figures represent (A) the mitochondria of the intact cells; (B) of the cells exposed to shock waves; (C) and (D) of the apex and base of the cells exposed to sound stimulation respectively.

In the intact cells, a number of dense, straight bands which are named the cristae mitochondriales (M_1) are visible inside some mitochondrial profiles. The cristae are not always visible distinctly at the resolution available, and show a considerable variation in shape according to the angle as which they are cut.

After exposure of the animal to oxygen deprivation, the mitochondria became in general lighter and swelled. The morphological changes in the mitochondrias of the outer hair cells were also apparent, when the animal was exposed to sound stimulation. However, in the base of the cells, the mitochondrias bear a very close resemblance to the intact mitochondria, and the appearance of the cristae (M_2) are in general normal. The appearance of mitochondria of the apex was more variable. While some appeared dense and structureless (M_3), others were rather normal (M_4). Furthermore, a number of dense granules were visible inside the mitochondrial profile (M_5). The substance of the granules may be very dense and the granules appear to be the small irregular agglomerations of grains. The mitochondrial structure was more severely affected during the sound stimulation. Some mitochondrias (M_6) swelled and became increasingly lighter, and simultaneously their granules become lighter and were arranged in large fuzzy formations.

Furthermore, it was observed that the mitochondrias (M_7) of the nervous system surrounding the basis of the outer hair cells remained normal after the sound stimulation.

Spoendlin[66] has already described the experiments to show the ultra-microscopic changes in the organ of Corti after exposure to noise (125 db). In his experiments, the first significant changes were found to be a marked increase in apical mitochondrial granules in the outer hair cell and swelling of the mitochondria in the nerve endings at the outer hair cells. However, according to the present results, it seems reasonable that the most early change in the outer hair cells caused by sound stimulation is the marked change of mitochondrial structure of the apex.

The histochemical study has been carried out in order to observe if any change in the dehydrogenase activity of the organ of Corti

may be caused by the exposure of 15 hours to sound stimulation (4000 c.p.s., 105 phon). In this experiment, guinea pigs were used. As seen in Figure 21, there existed no significant change in the dehydrogenase activity of the organ.

The same results were obtained in the experiments in which guinea pig breathed air containing 5 per cent oxygen for 30 minutes and in which the animal was exposed to shock waves. Furthermore, in the other experiments, it was also revealed that the marked swelling of the mitochondria of the stria vascularis and spiral ligament is not always associated with the marked loss of oxidative activity of these tissues.

Consequently, the present experimental data do not present the mutual dependence of structural integrity and dehydrogenase activity of the mitochondria. However, it is well known that the cochlear microphonic potentials decline after exposure of an animal to oxygen lack and to high level test tone. Thus, it seems probable that the morphological state of mitochondria of the apex of the outer hair cells may determine the capacity of the cells to function. On the basis of the biochemical result, described in the former section, oxidative phosphorylation may probably control the morphological changes in the mitochondrias of the outer hair cells. This is also suggested from the work of Lipsett and Corwin,[68,69] who regard the mitochondrial swelling as dependent on oxidative phosphorylation.

In the present experiments, the morphological changes in the mitochondria of the outer hair cells were more markedly manifested after the oxygen deprivation than after the sound stimulation. That is, the mitochondrias of the base of cells remained normal, while they became in general lighter and swelled after the oxygen deprivation. But, as shown in Figure 5, the oxigraphic study revealed that the decline of oxigraphic trace was more markedly manifested during the sound stimulation than during the oxygen deprivation. Thus, there exists a paradoxical phenomenon.

By means of an oxigraph, it is possible to observe that, even if the oxygen tension in the fluid remains constant, decrease in the flow velocity of fluid surrounding the Pt-electrode causes a marked decrease in the oxigraphic trace. This fact makes it impossible to measure quantitatively the oxygen tension in the labyrinth.

Presumably, the changes in the inner ear caused by the above sound stimulation consist of the decrease in both the oxygen tension and the flow velocity of the labyrinthine fluid.

COMMENT

The present work provides an approach to an understanding of the biochemical mechanisms involved in acoustic trauma. To our knowledge, systematic studies of this type have not yet appeared, although some sporadic reports have occurred in recent years, pointing to good prospects in such a line of approach.

As revealed by the present studies, sound stimulation and oxygen deprivation have similar effects, decreasing the oxygen tension in the inner ear or altering the conditions of the inner ear blood vessels. It appears likely, then, that in the absence of one of these stresses (i.e., oxygen deprivation) it would take larger degrees of sound stimulation to induce a shift of hearing, but that the combination of both stresses would yield shifts at lesser degrees of oxygen deprivation.

A survey of the literature showed that extensive studies[70,71] have been carried out concerning the effect of oxygen deprivation upon cochlear microphonics, from the standpoint of reversible or irreversible shifts. The combined effects of sound and oxygen deprivation upon the same phenomenon have also been investigated.[72] Thus, the decrease in the oxygen tension in the inner ear, caused by sound stimulation, is thought to contribute to the shift of hearing and to the morphological change in the organ of Corti.

The electron microscopic studies actually yielded important additional information concerning the locus of acoustic injury and the significance of both the oxygen deprivation and the sonic vibration. In the present work, the earliest changes apparently occurred in the apex of outer hair cells of the organ of Corti. In such a case, it seems reasonable that the decrease in the oxygen tension in the inner ear may be a subordinate factor of the onset of acoustic injury. Actually the ear of an animal as affected by the exposure to shock waves, but that this effect is not the combined effect of vibration and oxygen deprivation in the inner ear, but the effect of vibration alone.

Thus the peculiar behavior may lend support to the so-called "physico-chemical theory" of the onset of acoustic trauma.[73,74] This theory assumed that chemical reactions on the biological structures of the inner ear, e.g., denaturalization of protein, can be initiated by infinitesimal amounts of vibratory energy.

During the past years there have appeared numerous reports of oxidations, induced or accelerated by intense ultrasonic vibrations.

And quantitative studies of the oxidation of a chemical reagent in aqueous solution by cavitation produced at audible frequencies have been carried out by Flosdorf et al.[75] Their data indicates that the oxidations are accomplished through the production of activated oxygen in association with cavitation.

According to Hogeboom and Schneider,[76,77] the disruption of isolated liver mitochondria by means of intense sonic vibrations resulted in the release of a relatively large amount of soluble protein as well as in the activation to a varying extent of several enzyme systems associated with the intact particles. Of the enzyme systems studied, cytochrome oxidase and DPN-cytochrome reductase were affected to a relatively slight degree, and almost the entire succinoxidase activity was recovered in sedimentable fraction.

Thus it seems probable that the mitochondria may be affected rather by the mechanical forces than by the oxidation, during exposure to sonic energy. Then the question arises . . . "What is the first event following sonic vibration of the mitochondria of the hair cells?"

In recent years, Linnane[78] has reported that an electron transport particle was isolated from beef heart mitochondria after sonic oscillation and that its oxidative phosphorylation was accelerated by a soluble component (protein) which remains in the supernatant fluid after sedimentation of the above particle.

Thus it seems probable that decrease in the oxidative phosphorylation of the outer hair cells is the first event following sonic vibration. Of course, this should be followed by decrease in the respiration of the cells. In the former section, it has been described that oxidative phosphorylation is the limiting factor of the biochemical alteration of the inner ear tissues caused by oxygen deprivation.

Accordingly, on the basis of biochemistry, the cause of acoustic trauma is similar to that of inner ear disease caused by vascular accidents, since decrease in the oxidative phosphorylation plays a predominant role in the onset of both diseases.

SUMMARY AND CONCLUSIONS

1. The oxygen tension in both the inner ear and the brain cortex has decreased during the exposure of an animal to a higher level test tone, while shock waves had no effect.

2. One of the effects of a lower level test tone on the inner ear was an increase in the glucose content of perilymph. It is assumed that the increase reflects the changes in the circulatory conditions within the inner ear.

3. The metabolic activities of the inner ear tissues disappeared, after anaerobic incubation, in the order:

$$\text{oxidative phosphorylation} \rightarrow \begin{matrix} \text{loss of intracellular K} \\ \text{glycolytic activity} \rightarrow \text{succinate oxidation} \\ \text{DPN-linked oxidations} \end{matrix}$$

It is assumed that oxidative phosphorylation acts as the limiting factor of the metabolic alteration, during oxygen deprivation.

4. The electron microscopy and histochemical studies have revealed that the earliest changes in the outer hair cells caused by sound stimulation are the morphological changes of the mitochondrial structure of the apex, and that, under these conditions, oxidative phosphorylation probably controls the above changes.

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REFERENCES

1. Kemp, E. H.: A Critical Review of Experiments on the Problem of Stimulation Deafness. Psychol. Bull. 32:325, 1935.

2. Hamberger, C. A., and Hyden, H.: Cytochemical Changes in the Cochlear Ganglion Caused by Acoustic Stimulation and Trauma. Acta Oto-laryng. Suppl. 61:1, 1945.

3. Hamberger, C. A., Hyden, H., and Nilsson, G.: The Correlation Between Cytochemical Changes in the Cochlear Ganglion and Function Tests After Acoustic Stimulation and Trauma. Acta Oto-laryng. Suppl. 75:124, 1949.

4. Hammer, G.: A Quantitative Cytochemical Study of Shock Wave Effects on Spiral Ganglion Cells. Acta Oto-laryng. Suppl. 127:1, 1956.

5. Hammer, G.: On Quantitative Cytochemical Changes in Spiral Ganglion Cells After Acoustic Trauma. Acta Oto-laryng. Suppl. 140:137, 1957.

6. Mori, H.: Influences of Auditory Stimuli on the Spiral Ganglion Cells—with Special Reference to the Metabolism of the Nucleic Acid. Zibi Rhinsyo 52:153, 1959.

7. Mori, H.: Histochemical Studies on the Changes of Spiral Ganglion Cells Produced by Noise Exposure, Especially on Nucleic Acid Metabolism. Jap. Jour. Otol. Tokyo 62, Suppl. : 214, 1959.

8. Katagiri, S., and Ohashi, T.: A Study of the Nucleic Acid in the Inner Ear Tissues by Means of Microspectrophotometer (Experiments on Acoustic Trauma). Jap. Jour. Otol. Tokyo 62, suppl. : 210, 1959.

9. Bejdl, W., and Krejci, F.: Untersuchungen mit radioactivem p^{32} bei akustischem Trauma. Wien. Klin. Wshr. 65:837, 1953.

10. Yoshikawa, H.: Studies on Amino Acids in the Cerebrospinal Fluid and in the Inner Ear Fluid in Auditory Impairment. Jap. Jour. Otol. Tokyo 58:696, 1955.

11. Mizukoshi, O., Nakai, Y., Hayashido, H., Hyo, Y., and Yoshihiro, J.: Amino Acid Metabolism in the Inner Ear and Auditory Center. Jap. Jour. Otol. Tokyo 61, suppl.:186, 1958.

12. Ito, T.: Experimental and Clinical Studies on the Changes in Content of Some Enzymes in the Labyrinthine and the Cerebrospinal Fluid, as Affected by the Injury of the Auditory Organ. Jap. Jour. Otol. Tokyo 57:983, 1954.

13. Mizukoshi, O.: Cyto-Chemical Study on the Auditory Center. Jap. Jour. Otol. Tokyo 59:33, 1951.

14. Uno, M.: Study of Nucleic Acids in Auditory Center by Ultraviolet Absorption. Jap. Jour. Otol. Tokyo 61:827, 1958.

15. Martini, V.: Liberazione di sostanza acetilcolinosimile nella perilimfa dell 'orecchio interno del piccione durante la stimolazione sonora. Boll. Soc. Ital. Biol. Sper. 15:1102, 1940 (cit. by Gisselsson, L.[16]).

16. Gisselsson, L.: Experimental Investigation into the Problem of Humoral Transmission in the Cochlea. Acta Oto-laryng. Suppl. 82:9, 1950.

17. Koide, Y.: Introductory Studies on the Chemical-Physiology of the Labyrinth. Acta Med. et Biol. 6:1, 1958.

18. Vosteen, K. H.: Die Erschöpfung der Phonoreceptoren nach funktioneller Belastung; Experimentelle histochemische Untersuchung zur Frage der Schalltransformation im Innenohr. Arch. Ohren-usw, Heilk. u. Z. Hals-usw. Heilk. 172:489, 1958.

19. Misrahy, G. A., Hildreth, K. M., Shinabarger, E. W., Clark, L. C., and Rice, E. A.: Endolymphatic Oxygen Tension in the Cochlea of the Guinea Pig. J. Acoust. Soc. Amer. 30:247, 1958.

20. Koide, Y., Tajima, S., Konno, M., and Nakano, Y.: Further Studies on the Oxygen Tension in the Labyrinth. Jap. Jour. Otol. Tokyo 62, Suppl.:216, 1959.

21. Koide, Y., Konno, M., and Morimoto, M.: Studies on the Oxigraphic Measurement of the Oxygen Tension in the Labyrinth. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:348, 1958.

22. Beck, Chl., and Beickert, P.: Morphologische Veranderungen an der Schnecke des Meerschweinchens bei Sauerstoffmangel und Lärmbelastung. Arch. Ohren-usw. Heilk. u. Z. Hals-usw. Heilk. 172:238, 1958.

23. Gulick, W. L.: The Effects of Hypoxemia upon the Electrical Response of the Cochlea. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:148, 1958.

24. Kingsley, G. R., and Reinhold, J. G.: The Determination of True Glucose in Blood by Reduction of Ferricyanide. The Production of a Linear, Reproducible Color Without the Use of a Stabilizing Agent in Macro- and Microtechniques Suitable for Visual and Photoelectric Colorimetry. J. Lab. Clin. Med. 34:713, 1949.

25. Koide, Y., and Shiiya, M.: Studies on the Photometric Analysis of Submicrogram Quantities of Glucose (Ferricyanide-Ferric Iron Method). Niigata Med. J. 71:677, 1957.

26. Seymour, J. C., and Tappin, J. W.: The Effects of Sympathetic Stimulation upon the Cochlear Microphonic Potentials. Acta Oto-laryng. 42:167, 1952.

27. Seymour, J. C., and Tappin, J. W.: Some Aspects of the Sympathetic Nervous System in Relation to the Inner Ear. Acta Oto-laryng. 43:169, 1953.

28. Beickert, P., Gisselsson, L., and Löfström, B.: Der Einfluss des Sympathischen Nerven systems auf das Innenohr. Arch. Ohren-usw. Heilk. u. Z. Hals-usw. Heilk. 168:495, 1956.

29. Maruyama, N.: Experimental Observations on the Labyrinthine Blood Flow and the Hearing. Jap. Jour. Otol., Tokyo, 59:717, 1956.

30. Krejci, F., and Bornschein, H.: The Cochlear Microphonic Potentials During Sympathetic Stimulation. Acta Oto-laryng. 44:154, 1955.

31. Akiyama, N.: The Relation of the Cervical Sympathetic Chain to the Auditory Organ. Jap. Jour. Otol., Tokyo, 58:1242, 1955.

32. Hojo, M.: Experimental Study of the Effect of Cervical Sympathetic Ganglionectomy on the Internal Ear. Jap. Jour. Otol., Tokyo, 62:57, 1959.

33. Passe, E. R. G.: Sympathectomy in Relation to Ménière's Disease, Nerve Deafness, and Tinnitus. Acta Oto-laryng. 42:133, 1952.

34. Strong, M. S.: Dorsal Sympathectomy in Labyrinthine Disease. Arch. Otolaryng. 65:340, 1957.

35. Ballenger, J. J.: Surgical Treatment of Labyrinthine Disharmony. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:77, 1958.

36. Koide, Y., and Nagaba, M.: Unpublished.

37. Nogi, T.: Experimental-Cytological Study on the Epithelium of Stria Vascularis. Jap. Jour. Otol., Tokyo, 61:1174, 1958.

38. Chevance, L. G.: Preliminary Note on the Biochemical Aspect of the Stimulation of the Autonomic Nervous System of the Guinea Pig Cochlea. Acta Otolaryng. 45:509, 1959.

39. Kimura, R., and Perlman, H. B.: Arterial Obstruction of the Labyrinth. Part I. Cochlear Changes. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:5, 1956.

40. Heunnekens, F. M., and Green, D. E.: Studies on the Cyclophorase System. XI. The Effect of Various Treatments on the Requirement for Pyridine Nucleotide. Arch. Biochem. Biophys. 27:428, 1950.

41. Hunter, F. E., Davis, J., and Carlat, L.: The Stability of Oxidative and Phosphorylative Systems in Mitochondria under Anaerobic Conditions. Biochim. Biophys. Acta 20:237, 1956.

42. Glick, D.: Gasometric Techniques. Techniques of Histo- and Cytochemistry, Interscience Publ., Inc., New York, p. 313, 1949.

43. Schneider, W. C., and Potter, V. R.: The Assay of Animal Tissues for Respiratory Enzymes. II. Succinic Dehydrogenase and Cytochrome Oxidase. J. Biol. Chem. 149:217, 1943.

44. Lehninger, A. L., Hassan, ul. M., and Sudduth, H. C.: Phosphorylation Coupled to the Oxidation of Ascorbic Acid by Isolated Mitochondria. J. Biol. Chem. 210:911, 1954.

45. Trevan, J. W.: A Modification of the Deflection Balance for Use in Biochemical Laboratories. Biochem. J. 20:419, 1926.

46. Eränkö, O.: Quantitative Methods in Histology and Microscopic Histochemistry. S. Karger, Basel, p. 38, 1955.

47. Dixon, K. C.: A Study of Cortical Metabolism in Relation to Cerebral Disease. Brain 63:191, 1940.

48. Dixon, K. C.: Action of Potassium Ions on Brain Metabolism. J. Physiol. 110:87, 1949.

49. Dixon, K. C.: Anaerobic Leakage of Potassium from Brain. Biochem. J. 44: 187, 1949.

50. Mudge, G. H.: Studies on Potassium Accumulation by Rabbit Kidney Slices: Effect of Metabolic Activity. Amer. J. Physiol. 165:113, 1951.

51. MacFarlane, M. G., and Spencer, A. G.: Changes in the Water, Sodium and Potassium Content of Rat-Liver Mitochondria During Metabolism. Biochem. J. 54:569, 1953.

52. Davies, R. E.: Relations Between Active Transport and Metabolism in Some Isolated Tissues and Mitochondria. Symp. Soc. Exptl. Biol. 8:453, 1954.

53. McCabe, B. F., and Lawrence, M.: The Effects of Intense Sound on the Non-Auditory Labyrinth. Acta Oto-laryng. 49:147, 1958.

54. Mann, P. J. G., and Quastel, J. H.: Nicotinamide, Cozymase and Tissue Metabolism. Biochem. J. 35:502, 1941.

55. Racker, E., and Krimsky, I.: Effect of Nicotinic Acid Amide and Sodium on Glycolysis and Oxygen Uptake in Brain Homogenates. J. Biol. Chem. 161:453, 1945.

56. Barron, E. S. G., Miller, Z. B., and Bartlett, G. R.: Studies on Biological Oxidations. XXI. The Metabolism of Lung as Determined by a Study of Slices and Ground Tissue. J. Biol. Chem. 171:791, 1947.

57. Kornberg, A., and Lindberg, O.: Diphosphopyridine Nuceotide Pyrophosphatase. J. Biol. Chem. 176:665, 1948.

58. Pardee, A. B., and Potter, V. R.: Factors Affecting the Maintenance of Oxidative Phosphorylation in a Kedney Homogenate System. XI. The Effect of Various Treatments on the Requirement for Pyridine Nucleotide. Arch. Biochim. Biophys. 27:428, 1950.

59. Lester, R. L., Ziegler, D. M., and Green, D. E.: Studies on the Mechanism of Oxidative Phosphorylation. II. Role of Bound Pyridine Nucleotide in Phosphorylation. Biochem. Biophys. Acta 24:155, 1957.

60. Ernster, L., and Löw, H.: Reconstruction of Oxidative Phosphorylation in Aged Mitochondrial Systems. Exptl. Cell Research 3:133, 1955.

61. Ernster, L.: Organization of Mitochondrial DPN-Linked Systems. I. Reversible Uncoupling of Oxidative Phosphorylation. Exptl. Cell Research 10:704, 1956.

62. Krebs, H. A., and Kornberg, H. L.: A Survey of the Energy Transformations in Living Matter. Erge. der Physiol. Biol. Chem. u. Exptl. Pharmakol. 42:212, 1957.

63. Hogeboom, G. H., Claude, A., and Hotchkiss, R. D.: The Distribution of Cytochrome Oxidase and Succinoxidase in the Cytoplasm of the Mannalian Liver Cell. J. Biol. Chem. 165:615, 1946.

64. Ernster, L., and Lindberg, O.: Animal Mitochondria. Ann. Rev. Physiol. 20:13, 1958.

65. Harman, J. W.: Studies on Mitochondria: II. The Structure of Mitochondria in Relation to Enzymatic Activity. Exptl. Cell Research 1:394, 1950.

66. Spoendlin, H.: Submikroskopische Veränderungen am Corti 'schen Organ des Meerschweinchens nach akustischer Belastung. Pract. Oto-rhino-laryng. 20: 197, 1958.

67. Koide, Y., and Nakano, Y.: Unpublished.

68. Lipsett, M. N., and Corwin, L. M.: Studies on Stability of Rat Liver Mitochondria. I. Role of Oxidative Phosphorylation in Swelling. J. Biol. Chem. 234: 2448, 1959.

69. Corwin, L. M., and Lipsett, M. N.: Studies on Stability of Rat Liver Mitochondria. II. Relation of the Electron Transport System to Swelling. J. Biol. Chem. 234:2453, 1959.

70. Wever, E. G., Lawrence, M., Hemphill, R. W., and Straut, C. B.: Effects of Oxygen Deprivation upon the Cochlear Potentials. Amer. J. Physiol. 159:199, 1949.

71. Gulick, W. L.: The Effects of Hypoxemia upon the Electrical Response of the Cochlea. Annals of Otology, Rhinology and Laryngology 67:148, 1958.

72. Tonndorf, J., and Brogan, F. A.: Combined Effect of Sound and Oxygen Deprivation upon Cochlear Microphonics. Annals of Otology, Rhinology and Laryngology 64:392, 1955.

73. Angeluscheff, Z. D.: Ultrasonics and Progressive Deafness. Acta Oto-laryng. 45:7, 1955.

74. Angeluscheff, Z. D.: Sonochemistry and the Hearing Organ. Acta Oto-laryng. 46:386, 1956.

75. Flosdorf, E. W., Chambers, L. A., and Malisoff, Wm. M.: Sonic Activation in Chemical Systems: Oxidations at Audible Frequencies. J. Amer. Chem. Soc. 58: 1069, 1936.

76. Hogeboom, G. H., and Schneider, W. C.: Cytochemical Studies. II. Physical State of Certain Respiratory Enzymes of Mitochondria. J. Biol. Chem. 194:513, 1952.

77. Linnane, A. W.: A Soluble Component Required for Oxidative Phosphorylation by a Sub-Mitochondrial Particle from Beef Heart Muscle. Biochem. Biophys. Acta 30:221, 1958.

LII

EFFECTS ON ROUND WINDOW POTENTIALS OF LOCALIZED CHANGES IN COCHLEAR TEMPERATURE

ALFRED H. CHAMBERS, PH.D.

AND

GEORGE G. LUCCHINA, M.D.

BURLINGTON, VT.

Several investigators have described depression of cochlear potentials evoked by sound stimuli as a result of cooling the cochlea by various means. Adrian, Bronk and Phillips[1] observed weakening of these potentials in the guinea pig when ice was placed on the cochlea. Kahana, Rosenblith and Galambos[2] observed decrease in magnitude of these potentials in the hamster as a result of lowering body temperature as reflected by cheek pouch temperature. Bornschein and Krejci[3] observed a similar effect in the guinea pig as a result of holding dry ice on the cochlea for a brief time. Fernandez, Singh and Perlman[4] observed decrease in cochlear response in the guinea pig as a result of lowering body temperature, and under certain conditions they obtained an increase in the potentials as a result of raising body temperature. Reversibility of the effect on the cochlear response was reported by all these investigators.

The question arises whether cooling could be localized in the cochlea sufficiently to bring about great enough differences in cooling of different cochlear regions to demonstrate possible frequency-selective changes in cochlear potentials elicited by a wide range of frequencies. In 1956 the present authors[5] reported reversible frequency-selective depression of round window potentials by localized cooling of the cochlea. The experiments to be described are an extension of

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From the Department of Physiology and Biophysics, The University of Vermont College of Medicine, Burlington, Vermont. This investigation was done during the tenure by Dr. Lucchina of a postdoctoral fellowship (BF-8249) from the National Institute of Neurological Diseases and Blindness, Public Health Service. Part of this work was presented by Dr. Lucchina to the Faculty of the Graduate College of The University of Vermont in partial fulfilment of the requirements for the degree of Master of Science.

this work using a lower temperature to bring about depression of potentials more quickly, a wider range of stimulating frequencies and a recording technique which permits more rapid coverage of the entire range of frequencies. Cochlear regions in addition to the one previously reported have been cooled and some effects of localized warming have been observed.

METHODS

Cats anesthetized with sodium pentobarbital, 36 mg per kg, were used. Animals weighing 1 to 2 kg were preferred since with these the effects of cooling seemed to be somewhat more easily demonstrated than with larger (and older) animals. The bulla was exposed using essentially the approach described by Tonndorf.[6] Part of the wall of the bulla was removed. Cochlear potentials were recorded from a gold foil electrode on the round window membrane. The electrode consisted of a narrow strip of gold foil 2.5 or 7.5 micra in thickness, about 2 cm long, inserted in an 18 or 20 gauge hypodermic needle. The foil was held in place by a plug of wax pressed into the end of the needle with about 2.5 mm of the foil protruding from the tip; in use the electrode was positioned by a micromanipulator so that the free tip of the foil touched only the round window membrane. The reference electrode was an 18 gauge hypodermic needle inserted in the neck tissues. Potentials were amplified by a single-sided amplifier (designed by Dr. E. G. Wever of Princeton University) the output of which was led to a DuMont 247-A oscilloscope equipped with high voltage accelerator and were photographed on Kodak Linagraph 697 paper. The diffuse sound stimulus was from a Grass AM-3 audio monitor and loudspeaker, driven by an audio oscillator with sine wave output. The anesthetized cat was placed in a grounded wire screen cage acoustically shielded with spun glass insulation. The loudspeaker was placed outside the cage near one end which had a 6x10-inch opening in the spun glass; the front of the speaker was about 35 cm from the animal's ear.

Localized cochlear cooling was accomplished by placing on the bone over the cochlea the tip of a 2.5 cm long, 14 gauge copper wire soldered to the apex of a cone shaped brass cup of 7 cm altitude and 5 cm base diameter with a 2.5 cm long cylindrical rim soldered to the base. Alcohol cooled by dry ice to about −65°C was placed in this cup along with a small piece of dry ice. The temperature of the wire tip of the cooling device, measured by a copper-constantan thermocouple (30 gauge wire) soldered to the tip and a calibrated galvanometer, fell in about 1 minute to a minimum of about −40°C with the

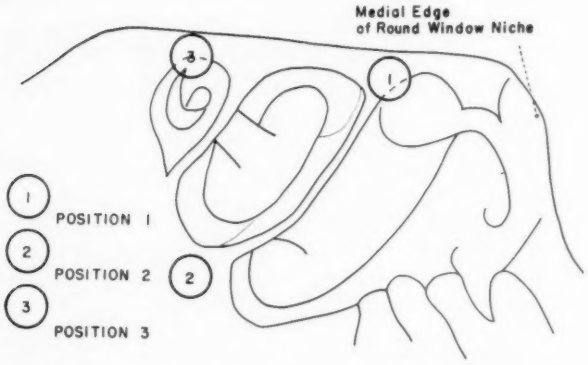

Fig. 1.—The three positions in relation to the cochlear turns underlying the bone. Apical turn at left.

device in air and about −32°C with the tip on bone over the cochlea. Rise of the temperature to precooling values after removal of the coolant was nearly complete in 5 minutes. In routine use the thermocouple was not on the wire tip. Observations have been made while cooling the following three positions on the bone overlying the cochlea. Figure 1 illustrates these three positions in relation to the turns of the cochlea underlying the bone.

Position 1. A region adjacent to the bony septum and about 2 mm from the round window niche. This corresponds to a region over the first coil as it comes around to make its first quarter turn.

Position 2. A region at the apex of the acute angle formed by the septum and the bulla tympanica on the petrous bone. This corresponds to a point about equidistant from the first and second coils as they both turn back into the petrous bone to make their last half turn and is identical with the position described elsewhere.[5]

Position 3. About 3 to 4 mm from the round window on the tympanic membrane side of the bony septum. This corresponds to a region over the apical turn of the cochlea.

The procedure of an experiment was as follows: with the recording electrode and cooling wire in place, cochlear potentials elicited by tones from 1000 to 10,000 cycles per second at 1000 cycle intervals were photographed as a control. Stimulus intensity was adjusted to

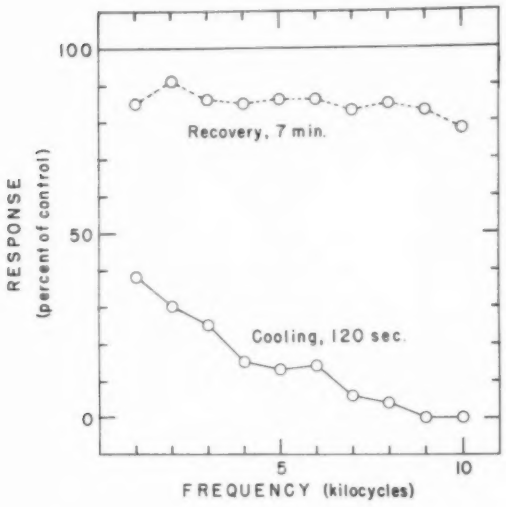

Fig. 2.—Effects on cochlear potentials during cooling and following removal of the coolant, cooling device at position 1.

yield an oscilloscope trace of convenient size for measurement. Potentials were well below the maximum value at each frequency. A single sweep of the oscilloscope beam was photographed at each tone, the paper being advanced by hand after each exposure. Sweep speed, constant throughout an experiment, was such that 5 or 6 complete cycles at the lowest frequency routinely used appeared in a single exposure. The coolant was then placed in the brass cup and 15 seconds afterwards potentials evoked by the series of 10 tones were again photographed. Such series of 10 exposures was repeated at 45, 75, 105 and sometimes 120 or 135 seconds; the time required to complete one series was about 12 seconds. Immediately after the last series the coolant was pipetted from the cup, leaving the wire in place, and additional series photographed at ¼, 1, 2, 7 and sometimes 12 minutes. Gain controls of all equipment remained constant throughout a complete experiment. A magnified image of the photographed potentials was projected by a reflectoscope, the peak to peak amplitude measured and, for each frequency, expressed as percent of control value. Absolute values of potentials were not routinely determined; a few such measurements indicated that, in general, control potentials were not greater than 1.0 to 1.2 mv with most less than this.

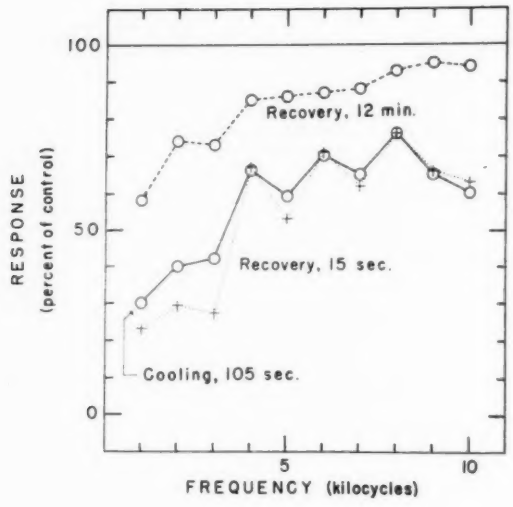

Fig. 3.—Effects on cochlear potentials during cooling and at two intervals following removal of the coolant, cooling device at position 2.

The response of the last tone in a series will of necessity represent that from a cochlea cooled about 12 seconds longer than when the first tone's response was photographed. During the initial stages of cooling when temperature gradients within the cochlea would be changing rapidly a response differential based on this time factor may be observed. In order to minimize this, those tones whose response was expected to change most according to the region cooled were first in the series. Thus when cooling position 1 the tones were sounded in the order 10,000 to 1000 cycles and vice versa during recovery; for positions 2 and 3 the reverse order was used. This time differential proved to be of considerable importance during the series at 15 seconds but of little or no effect during the series at 75 and 105 seconds. In most cases the patterns of depression of the two later intervals were similar to each other but differed from that of the first series.

Intracochlear temperatures during cooling were measured by inserting a copper-constantan thermocouple (30 gauge wire) into various regions of the cochlea, described later, through small holes drilled in the cochlear wall and through the round window membrane;

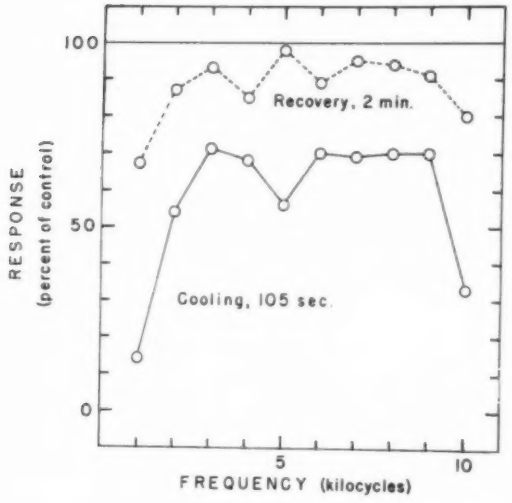

Fig. 4.—Effects on cochlear potentials during cooling and following removal of the coolant, cooling device at position 3.

readings were made with a Leeds and Northrup single range potentiometer indicator.

RESULTS

Controls. To determine the reproducibility of the method, potentials were measured with the cooling device in place, without adding coolant, at time intervals comparable to those in an experiment. In one such procedure 60 individual measurements made over a period of 9 minutes resulted in 59 within 10 per cent of control and 40 within 5 per cent; the single reading outside these ranges was −15 per cent.

Another experiment using a water and ice mixture, at position 1, instead of the usual cold alcohol resulted in the following: In three series done 2, 4 and 6 minutes after the start all potentials remained between 90 and 100 per cent of control except two which were 89 per cent. After an additional four minutes of cooling the responses to 9,000 and 10,000 cycle tones had fallen to 85 and 84 per cent, respectively, while responses to the other 8 tones remained within 2 per cent of their 6 minute value.

Temperature measurement by thermocouple on the tip of the hypodermic needle of the active electrode showed a temperature drop of about 1°C when the cold alcohol was placed in the cooling device with the copper wire separated from the electrode by about 3 mm. Direct cooling of the round window region by an electrode in close proximity to the cooling device could not have been a serious complication.

On numerous occasions disappearance of the potentials after death of the animal and their disappearance from ears damaged by accidental spillage of alcohol on the round window indicated that the magnetic field of the loudspeaker did not contribute directly to the potentials recorded.

Cochlear Cooling. Depression of potentials by cold and their recovery after removal of the cold alcohol in typical experiments are illustrated by Figures 2, 3 and 4 when the cooling device was on positions 1, 2 and 3 respectively. For the sake of clarity only one series measured during cooling and one during recovery (except for position 2) are included.

Cooling Position 1. Characteristic of results observed while cooling this position was greater depression of the response to the high frequencies than to the low frequencies. In addition in many instances the curves showed a rise (less depression) at 5, 6 and 7 kilocycles followed by a fall at the higher frequencies. In the curve of Figure 2 this rise, at 6 kilocycles, is just noticeable.

Such curves were observed on 15 of 21 cats. In 4 of these 15 this pattern of depression was not evident during cooling but appeared during recovery. In the six instances in which this pattern was not observed during either cooling or recovery, frequency-selective depression was still evident and in three instances resembled the curves obtained cooling position 2.

Cooling Position 2. With the cooling device on this position depression of the response to the lower frequencies occurred, with less depression to the 4 to 8 kilocycle range and with further depression to the two higher frequencies. In most instances depression at ten kilocycles was relatively greater than that illustrated in Figure 3, and in some cases as great as or slightly greater than that at low frequencies (Fig. 5). A greater depression at low frequencies relative to that at high frequencies for the series done 15 seconds after removal of the coolant is shown in the results illustrated in Figure 3.

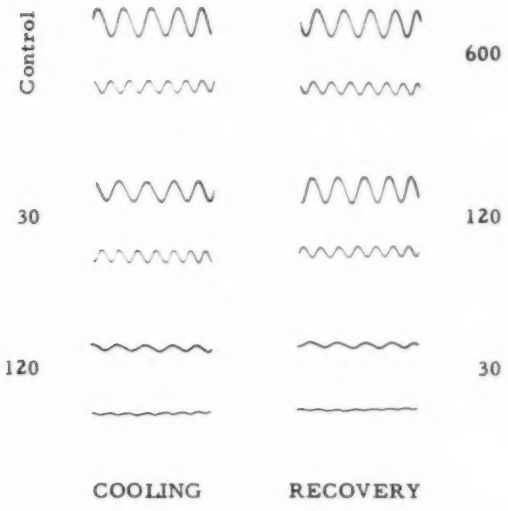

Fig. 5.—Cochlear potentials recorded during cooling and recovery from cooling. Figures are seconds after cold alcohol was added to or removed from cooling device at position 2. The top record of each pair is the response to a 2 kilocycle tone, the bottom to 10 kilocycles with sweep speed changed between. The control 2 kilocycle potentials are about 490 microvolts.

The pattern of depression developed during cooling is still very evident 12 minutes after removal of the coolant. Subsequent measurements before disturbing the electrode or cooling device were not made but comparison with control measurements made, after about ½ hour, as preliminary to a second experiment still showed this pattern.

Curves resembling the above description were obtained on 14 of 17 cats. There was a single instance in which the curve obtained cooling position 2 resembled the curve shown in Figure 2.

The average, for all cats, of the depression of the response to 1,000 cycles when position 1 was cooled was very close to that when position 2 was cooled; the difference between these averages was not statistically significant. On the other hand, the difference between these averages for tones from 3,000 to 10,000 cycles was statistically significant, depression being less for position 2 than for position 1. In the case of 2,000 cycles the difference, though in the same direction as for the higher frequencies, was not statistically significant. In

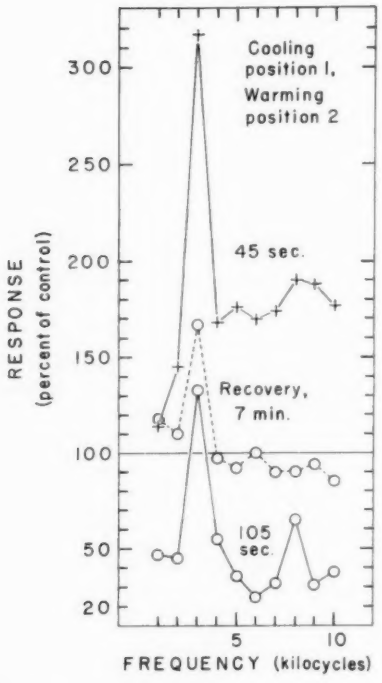

Fig. 6.—Effects on cochlear potentials at two intervals during simultaneous cooling of position 1 and warming of position 2 and following removal of the cold and warm liquids.

computing the averages, responses obtained after 75 seconds of cooling were used.

Figure 5 illustrates responses to 2 and 10 kilocycles during cooling position 2, and recovery, with the oscilloscope sweep adjusted to spread the response in each case. In this instance greatest depression was to 16 and 5 per cent of control for 2 and 10 kilocycles respectively, in the responses recorded 30 seconds after removal of the cold alcohol. Recovery of the responses to about 95 per cent of control is shown 10 minutes after removal of the coolant.

Cooling Position 3. This region of the cochlea was cooled in five cats. The steep initial slope is the principal difference between this

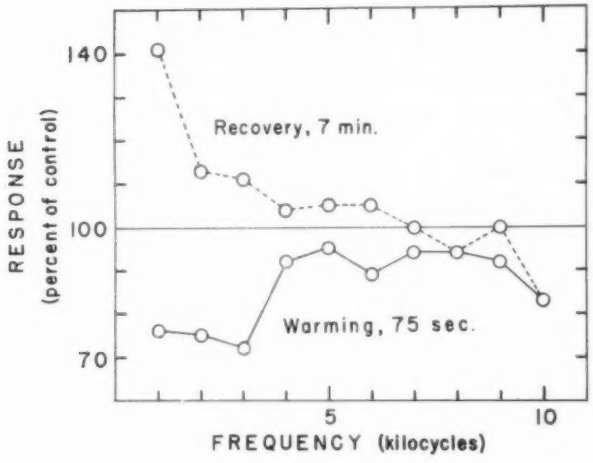

Fig. 7.—Effects on cochlear potentials during warming and following removal of warm water, device at position 1.

curve and those obtained by cooling position 2 and was observed in 2 of the 5 experiments. A curve of this appearance was not obtained in any of the experiments in which position 2 or position 1 was cooled.

Intracochlear Temperatures During Cooling. With a thermocouple inserted separately in each of the following regions, temperature measurements were made while each of the three positions was cooled in the usual manner:

T_1—Immediately inside the round window

T_2—Near the end of the first half turn of the first coil

T_3—Through the same opening for T_2 but pushed 3 to 4 mm apically along the cochlear coil

T_4—The apical coil (at position 3)

Temperatures were measured just before cooling, at 15 second intervals for 2 minutes during cooling, then, following removal of the coolant, at 15 second intervals for two minutes and at 1 minute intervals for an additional five minutes. In all instances cooling was rapid during the first 30 seconds, then proceeded more slowly until, in about one

minute, a temperature was reached which remained constant within 1 degree until the coolant was removed. After removal of the cold alcohol the temperature increased rapidly during the first minute then more slowly until a value equal to or very close to control was reached within seven minutes. The time differential in the response pattern observed during the series done early in the cooling period with relative unimportance of this factor in the later series probably is accounted for in large part by the time course of the intracochlear temperature.

Table I shows intracochlear temperatures reached after one minute of cooling. Temperatures just before cooling were 35°C ± 2°C and were from 2° to 5° below rectal temperature.

TABLE I

INTRACOCHLEAR TEMPERATURES (°C) REACHED AFTER 1 MINUTE OF COOLING WITH COOLING DEVICE ON EACH OF 3 POSITIONS

See text for description of thermocouple locations.

THERMOCOUPLE LOCATIONS	COOLING POSITION 1 CAT NO.			COOLING POSITION 2 CAT NO.			COOLING POSITION 3 CAT NO.		
	69	70	71	69	70	71	69	70	71
T_1	11	23	16	20	27	22	16	25	21
T_2	8	14	9	10	22	18	17	18	18
T_3	18	26	24	15	25	18	23	20	25
T_4	26	22		18	20		0	2	

Simultaneous Cooling of Position 1 and Warming of Position 2. Figure 6 illustrates results obtained in one cat in which position 1 was cooled in the usual way and position 2 heated by 75°C water in a second cone. The determinations made 45 seconds after placing the cold and hot liquids in the respective cones are included to show the initial rise of the response, followed by a fall at 105 seconds. Seven minutes after removal of the liquids the potentials returned nearly to control value except in the case of those for 3 kilocycles. During a repetition of this procedure later, on this animal, no noticeable response to 3 kilocycles could be elicited but an initial rise above control, followed by a fall, at 1 and 2 kilocycles was still observed. In this latter case the curve obtained at 105 seconds showed a response difference between the low and high frequencies more marked than that of Figure 2; seven minutes after removal of the water and alcohol a pronounced

rise above control of the response to 1, 2 and 4 kilocycles was observed.

Experiments on this animal before the illustrated results were obtained showed a curve when cooling position 2 similar to other position 2 curves and a curve when cooling position 1 similar to other position 1 curves except for somewhat less depression to 3 kilocycles than to 2 or 4 kilocycles.

Warming Position 1. A few experiments were done in which water at 40°C to 55°C was placed in the cone without simultaneous cooling of another position. Results in one case are presented in Figure 7 when 55°C water was used. There is a small degree of depression of the response to the lower frequencies and to 10 kilocycles during warming with a significant rise above control of the response to 1 kilocycle 7 minutes after removal of the warm water. This rise above control was also observed in this animal after using water at 40°C and 50°C. In each case this response had returned to or slightly below control within 30 minutes. When 45°C water was used this rise was less marked. The rectal temperature of this animal was 35.5°C to 35.8°C during these measurements.

No increases above control comparable to that in Figure 6 were observed.

COMMENT

The results indicate that cooling restricted regions of the cochlea depresses cochlear potentials elicited by various frequencies to different degrees and the pattern of this depression changes with the cochlear region cooled. Although the results shown in Figures 2, 3 and 4 were obtained from different cats, in some instances response curves like those illustrated for positions 1 and 2 were obtained by cooling these positions consecutively in the same animal. In the cat from which the curve in Figure 4 was obtained, a curve like that in Figure 3 was also observed when position 2 was cooled. Repeated cooling of a given position in the same animal, and recovery, was done in several instances; in many of these cases almost identical patterns of depression were observed.

Some of the variability in the results may be accounted for by the uncertainty of placing the wire tip of the cooling device on exactly comparable regions in different animals. In addition varying bone thickness over the cochlea in different animals could contribute to this variability. For instance, in drilling the cochlea to insert the thermocouple in cat 70, Table I, a markedly thicker bone was noticed and

at the same time intracochlear cooling in general was not as great in this animal.

Since our chief interest was in observing changes in cochlear potentials over short periods of time, rectal temperatures were not routinely measured as the change in this temperature over a 10 or 15 minute period would not be expected to be very great. Rectal temperatures were held between 35°C and 38°C in several animals, however, and no consistent difference was found between the patterns of depression of potentials in these cases and those in which the temperatures were not controlled. The degree of recovery likewise varied in those animals with controlled rectal temperatures as well as in those without such control.

UNIVERSITY OF VERMONT

REFERENCES

1. Adrian, D., Bronk, D. W., and Phillips, G.: The Nervous Origin of the Wever and Bray Effect. J. Physiol. 73:2P, 1931.

2. Kahana, L., Rosenblith, W. A., and Galambos, R.: Effect of Temperature Change on Round-Window Response in the Hamster. Am. J. Physiol. 163:213-223, 1950.

3. Bornschein, H., and Krejci, F.: Elektrophysiologische Untersuchungen über Temperatureffekte in der Schnecke. Acta Oto-laryng. 45:467-478, 1955.

4. Fernandez, C., Singh, H., and Perlman, H.: Effect of Short-Term Hypothermia on Cochlear Responses. Acta Oto-laryng. 49:189-205, 1958.

5. Chambers, A. H., and Lucchina, G. G.: Reversible Frequency-Selective Reduction by Cold of Round Window Potentials. Fed. Proc. 15:33 (Mar.) 1956.

6. Tonndorf, J.: Surgical Approach to the Bulla Tympanica in the Guinea Pig, Rabbit, Cat, and Dog. Air University School of Aviation Medicine, Project Number 21-27-001, Report Number 4 (Apr.) 1952.

LIII

ETIOLOGY OF UNILATERAL TOTAL DEAFNESS

STUDIED IN A SERIES OF CHILDREN AND YOUNG ADULTS

G. EVERBERG

COPENHAGEN, DENMARK

Group studies of school children reveal in a few cases total deafness in one ear with normal hearing in the other, unexplained by the history or objective findings. Investigation of a large series of persons with unilateral deafness is required to throw a light on the etiology.

The present paper submits the conclusions drawn on the basis of an investigation of 122 children and adolescents having total deafness in one ear and normal hearing in the other. In this connection, evident cases of labyrinthine lesion, due to fracture or operation, will be disregarded, as they are of no etiological interest.

Unilateral total deafness has been ascribed to endogenous as well as exogenous factors.

Hereditary unilateral deafness seems to have been discussed in only one paper: Smith, in 1939,[31] reported a family with total unilateral deafness in nine persons of four generations. Four were deaf in the right ear and four in the left, while the side was unknown in one case. All nine had completely normal hearing in the opposite ear. Among eight siblings, four were affected, two on the right and two on the left. A maternal aunt of the principal subject was deaf-mute, allegedly following measles; the youngest of her three children had unilateral deafness and the second of her three grandchildren was born deaf.

Exogenous Factors. The best known exogenous factor is mumps. Deafness due to mumps has been known for the past 100 years. After Toynbee[32] had pointed out that mumps might give rise to sudden, unilateral deafness, numerous case reports appeared. From these re-

From the Ear Clinic, Copenhagen City Hospital.

ports[14] it is apparent that in four-fifths of the cases the deafness is unilateral, that its onset is fairly acute, frequently accompanied by tinnitus, vertigo, and vomiting.

Sudden "idiopathic" deafness may occur in children and young adults. This was what had happened in 13 out of 110 cases (12%) reported by Bierman.[10]

The literature contains only two publications reviewing the etiology of unilateral deafness in children. Marschak[27] reported 50 cases of unilateral deafness. In 27 "even the otoscopic evidence pointed with all likelihood to a tympanogenic etiology." Of the remaining 23, 16 were interpreted as acquired and seven as congenital. Out of the 16 acquired cases seven were attributed to measles, four to mumps, two to influenza, and three to epidemic meningitis.

Marschak assumed that there was a familial predisposition to nerve deafness, but it is not sufficiently clear to what extent this assumption is based upon genetic studies instead of a family history.

Kinney[23] briefly reviewed 310 cases of unilateral deafness. As a probable cause he reports meningitis in 23.9%, as a possible cause measles in 23.2%, and mumps in 10.6%. In 42.3% the etiology was entirely unknown. The series did not include hereditary cases.

PRESENT INVESTIGATIONS

As already mentioned, the series consists of 122 children and young adults, aged 7 to 21 years, with total deafness in one ear and normal hearing in the other. In a previous paper[18] dealing with the clinical features of unilateral deafness, the author has described the selection of the series, diagnostic methods, and results. The clinical-etiological investigation was based on a thorough history, general otological investigation, tests of acoustic-vestibular function, radiography, and genetic studies.

Both endogenous and exogenous etiological factors were demonstrated.

ENDOGENOUS FACTORS

The endogenous factors believed to contribute to this disorder have been previously discussed[13,15,16] by the author, and only the main features will be sketched here in brief outline:

Any form of hearing loss among the relatives of the subject was inquired into in 108 families by questioning the parents and sending questionnaires to other members of the families. The questionnaires were returned by 90.3%. The others were believed to have normal hearing. In the remaining 14 families, this procedure proved impracticable because of illegitimacy, emigration, and adoption, among other reasons. Allegedly, hardness of hearing did not occur in these families.

A total of 165 relatives, who confirmed hearing loss or who were pointed out as being hard of hearing by the parents of the subject, were examined by the author. In 122 the hearing loss was due to the sequelae of otitis media, presbycusis, or noise. The remaining 43 exhibited endogenous perceptive disease of varying degree, manifesting itself as unilateral total deafness in 13 and in the remaining 30 as unilateral or bilateral, sometimes progressive varieties of neurolabyrinthopathy (NLP), often co-existing with all degrees of hearing loss within the same family as apparent from the following examples illustrated by abstracts of the pedigrees (numbered as in two previous papers[13,16] on hereditary unilateral deafness).

More than one case of unilateral deafness in the same family was found in 12 out of 122 families (about 10%), but it was in only seven families that it was the only perceptive lesion in the family (about 6%). Endogenous perceptive disease was present in a total of 30 families (about 25%).

In a few families there were endogenous as well as exogenous, possibly synergistic, factors as is evident from Figure 2.

It may be stated that no instance of consanguinity was found among the parents of the 122 subjects.

EXOGENOUS FACTORS

Inquiry into exogenous factors, brought to bear during pregnancy and delivery, proved negative.

The pregnancy had been, practically speaking, normal in all 122 cases. In two there was a history of short-lasting vaginal bleeding during the third month, in another two severe leg edema, but no proteinuria or hypertension. One of the mothers had a history of mumps without complications in the sixth month. No mother had suffered from rubella during pregnancy and none of them from syphilis, and indeed no clinical signs were found among the children, the

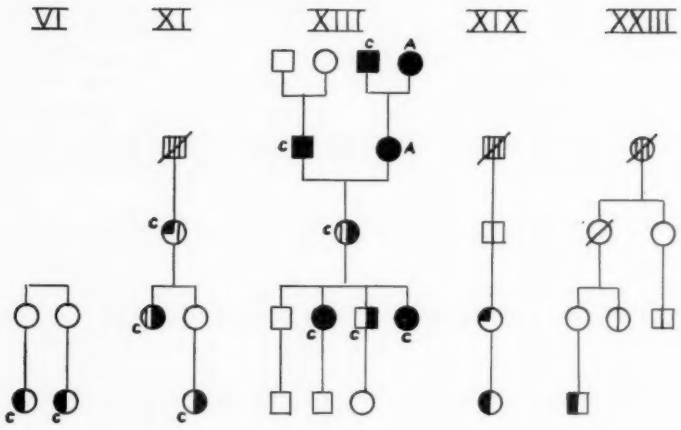

Figure 1

Presumed hearing of the perceptive type in deceased relative

Hearing impairment of the perceptive type, bilateral, symmetric

Deafmutism (C = congenital, A = acquired)

Right-sided total deafness

Left-sided subtotal deafness

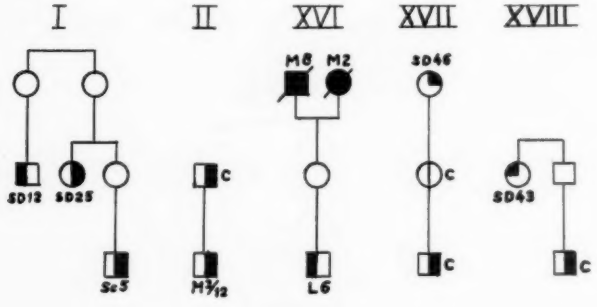

Figure 2

SD 12 Sudden idiopathic deafness at the age of 12
M 8 Meningitis at the age of 8
L = Labyrinthitis Sc = Scarlet fever C = congenital

Wassermann reaction being negative in all 108 cases so tested. Eight of 83 mothers with Rh positive children were Rh negative. This corresponds to the findings in a normal section of the population.[21] Only one Rh negative mother with an Rh positive child had traces of antibody at the time when the author saw her (the infant had not, however, shown any signs of erythroblastosis foetalis).

Delivery and post-partum period had been on the whole normal. Mild secondary uterine inertia had occurred in four patients and forceps delivery in three, but without difficulties and without leaving any traces of the forceps. Breech presentation had occurred in one patient.

Birth weight was in six cases, i.e., 4.9% 2500 gm or less (two weighing 2000 gm, two 2500 gm, one 2250 gm and one 2450 gm). According to W.H.O.'s Expert Group on Prematurity,[38] all newborn infants weighing 2500 gm or less are considered premature. According to the Medical Report for the Kingdom of Denmark 1957,[28] 6% of the infants born in the whole country weigh 2500 gm or less at birth. Thus, the present series did not contain an excess of prematures.

In eight instances, or 6.5%, the birth weight was more than 4000 gm, a maximum of 5000 gm. In Anderson's[5] analysis of the birth weight of 3389 infants, the corresponding weight group represented 6.4%–. In other words, the author's series also does not contain an excess of children having a birth weight higher than average.

Among the entire series 41.8% were first-born children. This percentage does not differ from normal which is about 38% in Copenhagen among the younger age groups.

EXOGENOUS FACTORS STEMMING FROM DISEASES DURING CHILDHOOD

AURAL DISEASES

Otitis media had occurred in 32%. By way of comparison, it may be mentioned that the frequency of otitis media in all ten grades of a normal school (200 pupils aged 7 to 16 years) was found to be 30% according to the diseases recorded on the school health cards. In order to ascertain the possible significance of otitis during early childhood (when complications might be imagined to have been obscured by other disease), the occurrence of otitis during pre-school age was investigated in cases where hereditary factors were not demonstrable.

TABLE I

INCIDENCE OF OTITIS MEDIA BEFORE SCHOOL AGE

	CHILDREN WITH UNILATERAL DEAFNESS (NON-HEREDITARY)		CONTROL GROUP
History of otitis during pre-school age in %	On deaf side	28	27
	On good side	21	

The result is shown in Table I in which 200 children from the first grades of two normal schools serve as controls.

After having considered the occurrence of otitis on the whole, let us proceed to investigate the complications.

Labyrinthitis. There was one definite case of otogenous, destructive labyrinthitis:

CASE 16. A six-year-old boy, who had previously had normal hearing, was admitted with acute, right-sided otitis of four days' duration, complicated by labyrinthitis involving severe vertigo and spontaneous nystagmus directed to the left. Hearing and vestibular function were present on admission, but were extinguished within a few days. His maternal grandfather and grandmother had lost their hearing during meningitis at the age of eight and two years respectively (Family XVI, Fig. 2). In addition to extinguished hearing and vestibular function, the author also found x-ray signs of obliterated semicircular canals.

In another case the deafness may possibly have been caused by otogenous labyrinthitis:

CASE 31. A two-year-old boy was admitted with bilateral acute otitis and mastoiditis. Bilateral mastoidectomy with clearing of the osteitis on the left as far as the superior arcade of the semicircular canals. After the operation, there was nystagmus directed to the right. Deafness was discovered at the first examination by the school doctor. The author found extinguished hearing and vestibular function as well as x-ray signs of obliterated semicircular canals on the deaf side.

Meningitis had occurred in five instances as a complication of otitis and in six cases in the form of epidemic cerebrospinal meningitis. In two cases, the deafness had been detected immediately after this disease, while in the remaining cases it was discovered by chance at school examination two to ten years later.

RELEVANT DATA FOR 11 PATIENTS WITH A HISTORY OF MENINGITIS

CASE 32. A five-year-old girl, who had previously had normal hearing, was hospitalized in a comatose state with left-sided acute otitis, mastoiditis, and men-

ingitis. In the spinal fluid 22,360 cells as well as type I pneumococci (aural discharge not submitted to bacteriological study). Left-sided mastoidectomy. At discharge, total deafness on the left was diagnosed. The author also found extinguished vestibular function and x-ray signs of obliterated semicircular canals.

CASE 33. A seven-year-old boy, who had previously had normal hearing, was admitted with left-sided, acute otitis, mastoiditis, and incipient signs of meningitis (neck stiffness, 87 cells in the spinal fluid). Left-sided mastoidectomy. Hearing had been greatly impaired on admission and was found to be extinguished on discharge at which time vestibular function had been lost also. The author found x-ray signs of obliterated semicircular canals.

CASE 34. A four-year-old boy was admitted with bilateral, acute otitis media, mastoiditis, and meningitis. Staphylococcus albus in the aural discharge. Spinal fluid 3,600 cells, but no bacteria. Bilateral mastoidectomy was carried out. At seven years of age, total right-sided deafness was detected by the school doctor. The author found extinguished vestibular function and x-ray signs of obliterated semicircular canals on the same side.

CASE 35. A five-year-old girl was admitted with bilateral acute otitis and meningitis. Spinal fluid: 7,200 cells and type I pneumococci (aural discharge not submitted to bacteriological study). At the age of seven right-sided total deafness was detected by the school doctor. The author also found extinguished vestibular function on the same side.

CASE 36. A boy, aged two, was admitted with bilateral otitis and meningitis. In the spinal fluid 68,400 cells and type 4 pneumococci (aural discharge not submitted to bacteriological study). At the age of about seven years, total deafness on the left was detected. When seen by the author the boy was also found to have extinguished vestibular function and x-ray signs of obliterated semicircular canals on the same side.

CASE 37. A boy, aged two, was admitted with right-sided acute otitis and meningitis. In the spinal fluid 25,000 cells and meningococci. In the aural discharge type 6 pneumococci. Right-sided paracentesis. Right-sided total deafness was detected by the school doctor at the age of seven.

CASE 2. A boy, aged three months, was admitted with bilateral acute otitis and meningitis. Spinal fluid: 39,000 cells and meningococci. Reduced mobility of the left corner of the mouth. When the boy was seven, the school doctor detected total deafness on the left. His father was totally deaf in the same ear, presumably from birth. Otoscopy normal (Family II, cf. Fig. 2).

CASE 38. A boy, aged two years, was admitted with epidemic cerebrospinal meningitis. Spinal fluid: 2,325 cells and meningococci. Normal otoscopic findings. At the age of ten years total deafness on the right was diagnosed by the school doctor. The author also found extinguished vestibular function on the same side.

CASE 39. A boy, aged two years, was admitted with epidemic cerebrospinal meningitis. Spinal fluid: 16,128 cells and gram negative diplococci. Normal otoscopy. The school doctor diagnosed right-sided total deafness when the boy was seven years of age. The author also found extinguished vestibular function and x-ray evidence of obliterated semicircular canals on the same side.

CASE 40. A boy, aged five months, was admitted with epidemic, cerebrospinal meningitis. Spinal fluid 9,000 cells and gram negative diplococci. Normal otoscopic findings. At the age of six years, total deafness on the right was detected acciden-

tally (telephoning). The author also found extinguished vestibular function on the same side.

CASE 41. A girl, aged four years, was admitted with purulent meningitis. Spinal fluid: 4,000 cells, but no growth of bacteria on culture. Normal otoscopic findings. The hearing was not tested in each ear separately. At the age of ten years, left-sided total deafness was discovered by the school doctor.

CHILDHOOD DISEASES

When inquiring into the possible significance of ordinary childhood ailments during early childhood, the author compared the frequency of pre-school childhood diseases among patients in whom no hereditary factors were demonstrable with the corresponding diseases in a control group of 200 children from the first grade of two normal schools where these diseases had been recorded on the school health cards when the children entered school.

TABLE II

INCIDENCE OF CHILDHOOD DISEASES

CHILDHOOD DISEASES DURING PRE-SCHOOL AGE	CHILDREN WITH UNILATERAL DEAFNESS (NON-HEREDITARY) %	CONTROL SERIES %
Mumps	32	36
Measles	72	75
Whooping cough	64	64
Chicken pox	52	59
Rubella	42	39
Scarlet fever	6	6

Thereupon, we shall proceed to the complications. According to the histories, two of the listed diseases appear to have been of significance to the unilateral deafness, viz., mumps and scarlet fever.

RELEVANT DATA FOR FIVE PATIENTS IN WHOM MUMPS MAY HAVE BEEN RESPONSIBLE

CASE 42. A boy, aged nine, previously seen by the author because of left-sided chronic otitis media with a hearing loss of about 30 db. During mumps the hearing in the left ear suddenly deteriorated, and one week later the author diagnosed total deafness.

CASE 43. A girl, aged nine, previously with normal hearing, who had suffered from mumps accompanied by fever, vomiting, vertigo, and tinnitus nine months

before she was seen by the author. Since that time, the hearing in the right ear had been impaired, and the next otological examination at school revealed total deafness. The parotitis complement fixation reaction was still strongly positive when the girl was seen by the author.

CASE 44. A boy, aged seven, complained of inability to hear with his right ear after mumps accompanied by severe vertigo. Otological examination one month later revealed total deafness.

CASE 45. A boy, aged five years, failed to react when addressed from the left side after mumps accompanied by fever and vomiting. Otological examination about one month later disclosed total deafness.

CASE 46. A boy, aged 11 years, suddenly ("with a click") lost the hearing in the right ear during an attack of mumps. The next otological examination at school revealed total deafness.

SCARLET FEVER

The following case has previously been reported by the author.

CASE 1. A boy, aged 11 years, suddenly developed unilateral deafness during scarlet fever. In addition, there was presumably a hereditary factor, as this patient's maternal aunt and her cousin had suddenly developed unilateral deafness of unknown cause in their 'teens and twenties respectively (Family I, Fig. 2).

HEAD INJURIES

Evident cases of labyrinthine lesion, due to fracture (one case) or operation (one case) were left out, as mentioned in the introduction, as being of no etiological interest.

Among the 122 patients with unilateral deafness, a total of 21 had a history of head injury, occurring in 12 prior to the detection of the deafness and in nine after.

HEAD INJURIES BEFORE DETECTION OF DEAFNESS

a) *Involving Unconsciousness.* Particular interest attaches to a case which has been reported separately and which therefore will be summarized only briefly here:

CASE 47. A boy, aged two and one-half years, fell, head first, down some stone steps and was admitted as a case of "mild concussion." From the age of three he suffered from attacks of vertigo and vomiting precipitated by certain sudden movements of the head to the left. At the age of four years, total left-sided deafness was disclosed. During two severe attacks, the author observed pronounced horizontal-rotatory nystagmus directed to the right. After the attacks the vestibular function was normal. From the age of 10 to 14 the attacks were accompanied by swelling of the parotid gland. From 14 years of age, he did not have any

attacks at all. Follow-up at 17 revealed extinguished vestibular function on the left.

In addition to this patient, there were two questionable cases of concussion at the age of two and three years respectively, observed in hospital for a few days. The deafness was detected by chance at the age of ten and six years.

b) *Unaccompanied by Unconsciousness.* Nine cases of head injuries of various kinds, sustained when falling from moderate height (table, beating stand for carpets, car) and in one case when run over (involving mandibular fracture). The deafness was not in any case detected in connection with the trauma.

HEAD INJURIES AFTER DETECTION OF DEAFNESS

a) *Involving Unconsciousness.* Four cases, three of whom were seen by a doctor and treated at home and one admitted to hospital.

b) *Unaccompanied by Unconsciousness.* Five sustained by falls, etc., followed by vomiting in one.

SUDDEN IDIOPATHIC DEAFNESS

One of the subjects had the following history:

CASE 48. Without preceding or concomitant disease a ten-year-old boy suddenly one day in his home developed left-sided deafness and severe tinnitus. Subsequent otological investigation revealed total deafness on the left.

COMMENT

It is not surprising that mumps has so far been considered so important a factor in the etiology of unilateral deafness. A dramatic course in an oriented patient (unlike the meningitic patient) has often been observed by the doctor, from the onset of tinnitus until the total loss of hearing. In such cases one can, so to speak, witness the cause of the deafness. Other causes of unilateral deafness, be they endogenous or exogenous, usually escape detection and are seldom demonstrable with certainty. Such causes may be inquired into and their probable existence may be demonstrated statistically. Thus, if a disease, such as meningitis, is materially commoner among patients with unilateral deafness than among a normal section of the population, this disease must be considered to be presumably the etiological factor.

If perceptive lesions are considerably commoner among the relatives of patients with unilateral deafness than in a normal section of the population, there is presumably a genetic relationship between these perceptive lesions and the unilateral deafness.

In the purely comparative and retrograde inquiry into the causes of a disease, it must be realized that as a rule one is operating merely with probable causes.

ENDOGENOUS FACTORS

In tracing endogenous factors of unilateral deafness, the frequency of neurolabyrinthopathy (NLP) of different varieties encountered among the relatives of the patient was compared with the frequency of perceptive lesion in the normal population.[9,16,22] Unilateral total deafness and deaf-mutism were found to be six to seven times commoner than expected and partial NLP about 11 times commoner than expected normally. Statistical significance was found, P being less than 0.2% for unilateral total deafness, less than 2% for deaf-mutism, and less than 0.1% for partial NLP. Thus, endogenous factors were more important than indicated by the inquiry into unilateral total deafness among the members of the families. There was more than one case of unilateral total deafness in only 12 out of the 122 families (about 10%), but endogenous perceptive lesions of different severity were present in more than twice this proportion, or 30 families (about 25%). Previous studies on families in which unilateral total deafness, deaf-mutism, and partial NLP have co-existed support the interpretation of a genetic relationship in the present findings which indicate that in about 25% of the cases unilateral deafness was hereditary. Presumably, there was a question of irregular dominant heredity, as the disorder did not occur in consanguineous marriages. However, unilateral deafness is rarely a genetic entity. More than one case occurred in 12 out of the 122 families, while in seven families (less than 6%) it was the only perceptive disease. It was not exactly the unilateral deafness which was transmitted in the remaining 23 families, but merely the dominant perceptive disorder with a particularly labile penetrance. It is perhaps the latter which decides whether unilateral deafness is to be the only perceptive disorder in the family, when the penetrance is low, or whether it is to co-exist with other varieties of NLP, when the penetrance is high.

In a few families (I, II, XVI, XVII, XVIII), however, the labile penetrance was not the only phenomenon. There might also be a sort of "predisposition" to acquired deafness. The same findings were

made by Lindenov[26] and Kristensen[25] in the case of sporadic, recessive deaf-mutism.

Within the hereditary group, one family is worthy of particular attention. True, the endogenous hearing loss of the perceptive type was not observed in other members than the subject, although her labyrinthine disease was probably of hereditary nature. This family has been reported previously,[12] but the follow-up on the involved relatives on occasion of the continued investigations into unilateral deafness necessitated a revision of the diagnostic results and conclusions.

The principal subject in this family, a 19-year-old girl, exhibited left-sided total deafness and loss of vestibular function on both sides. Her twin sister, who was monozygotic judging by all the findings—int. al. blood grouping—had normal hearing, but extinguished vestibular function on the right. A paternal aunt, also with normal hearing, had extinguished vestibular function on the left. On x-ray films it had previously been difficult to differentiate the cavities of the semicircular canals in the twins. Supplementary polytomography five years later, however, showed normal conditions. X-ray films of the paternal aunt also showed normal inner-ear appearances. Accordingly, the previously advanced presumption regarding the contributory role of exogenous factors in the labyrinthine abnormality cannot be maintained.

EXOGENOUS FACTORS

As evident from the pregnancy and delivery data in this series, there were no prenatal, natal, or neonatal factors to explain the unilateral deafness.

Exogenous factors in childhood consist primarily in certain infections, affecting the labyrinth or its immediate neighborhood. As stated above, the frequency of otitis media was no higher than might be expected, but its severity was striking.

Labyrinthitis may be tympanogenous as well as meningogenous. In the rare cases where acute, suppurative otitis gives rise to labyrinthitis (as in Case 16 and possibly also Case 31), the mechanism is as follows: the infection, usually during the first days, forces its way through one of the windows, generally the round window.[39] Regardless of the pathogenesis of labyrinthitis, healing may sometimes result

in osseous obliteration of the inner-ear cavities (as in Cases 16 and 31 to 34, 36 and 39; cf. also Everberg[17]).

Meningitis is the commonest cause of severe degrees of acquired perceptive disease in childhood,[6] but as a rule the hearing loss is bilateral, asymmetric, and partial. This applied to 93.5% of Trolle's[33] series comprising 46 persons with perceptive disease out of 313 patients followed up after meningitis. On the other hand, only three had total deafness in one ear with normal hearing in the other. Thus, total unilateral deafness is seldom a sequel to meningitis. This is presumably the explanation of the widespread, but erroneous view that meningitis is very seldom among the causes of unilateral deafness. In Marschak's and Kinney's analyses on the etiology of unilateral deafness, meningitis was blamed in 6% and 24% respectively. Out of the present patients 11 or 9% had a history of meningitis. The following findings may be considered for comparison: from Blegdamshospitalet, Frederiksberg Hospital, and the pediatric services of the Copenhagen hospitals, a total of 580 patients were discharged during the decade 1947-1956 following purulent, non-tuberculous meningitis (including meningococcal meningitis). The area served by these hospitals is somewhat larger than the metropolitan area, having a population of about 1.1 million in the middle of the period. This gives a frequency of 0.5 survivors from meningitis in 1,000 of the populaton. In other words, the incidence of meningitis in the present series is 180 times that in the population section from which the series is drawn. It may be concluded, therefore, that meningitis is an outstanding factor in the etiology of unilateral deafness.

Total deafness following meningitis is generally due to meningogenous labyrinthitis, since inflammatory involvement of the acoustic nerve is more liable to leave partial hearing loss.[11] Epidemic cerebrospinal meningitis involves the labyrinth with particular frequency, and is of particularly acute onset in young children due to the greater patency of the paths leading to the labyrinth (especially the cochlear aqueduct). It is worth emphasizing in this connection that the five cases of meningococcal meningitis in the present series had occurred in the age range three months to two years and the remaining cases of meningitis between three and eight years of age.

Ordinary childhood diseases were not commoner in the present series than in a corresponding control series (Table II).

Mumps may have been responsible in the five reported cases, but the causal relationship is far less certain than in the cases of meningitis

in which the connection was evident merely from the frequency. And unlike the cases of meningitis, the history of mumps could not be sufficiently substantiated. Two of the five patients had not even been seen by a doctor during the course of the disease.

The author made every effort to confirm the history of mumps by interrogation regarding the symptoms, bearing in mind particularly the mistake for febrile cervical adenitis.

The deafness had not in any case been recognized in immediate connection with the mumps, but not until some time afterwards. Probably, it cannot be ruled out that it may have been present also before the mumps and recognized accidentally afterwards. It was only in one case that the hearing before the mumps was known, viz., in a patient with chronic otitis on the side where the hearing was lost during mumps, so that a certain predisposition cannot be ruled out.

On the basis of the available data it seemed justified to regard mumps as a possible cause of the deafness in these five cases. In several other cases, the deafness had been attributed elsewhere to mumps, but none of the patients had exhibited hearing loss in connection with the mumps. Apparently, unilateral deafness is often ascribed to mumps only because this cause is known and because other causes do not seem immediately detectable.

Scarlet fever was mentioned as a possible etiological factor in the principal subject of Family I, where there was also a hereditary basis.[13] In this case too, however, the patient may have been deaf prior to the disease which has then merely been the occasion on which the deafness was detected. Scarlet fever does not appear to have been reported as the cause of unilateral total deafness (except in cases complicated by labyrinthitis), but the possibility is mentioned by Watkyn-Thomas in 1939.

Head injury as a factor in the etiology of unilateral deafness in the present series may be considered 1) on the basis of our knowledge about the effect of different head injuries upon hearing, 2) by comparing the frequency of concussion in the present series with its frequency in a comparable group, and lastly 3) by comparing the frequency and severity of head injuries on the whole in this series, occurring before and after the deafness was recognized (the same series serving as a control).

Re 1. Although total unilateral deafness is generally not caused by head injury except those involving fracture of the temporal bone,

TABLE III

ACQUIRED CAUSES OF UNILATERAL DEAFNESS

	DEFINITE	PROBABLE	TOTAL	% OF ACQUIRED CASES	% OF TOTAL SERIES
Meningitis	2	9	11	52.3	9.1
Mumps		5	5	23.8	4.1
Labyrinthitis (otogenic)[1]	1	1	2	9.5	1.6
Scarlet fever		1	1	4.8	0.8
Injury		1	1	4.8	0.8
Sudden idiopathic deafness[2]			1	4.8	0.8
			21	100.0	17.2

[1] Without meningitis

[2] Acquired case, unknown etiology

total deafness may result without the presence of fracture. This applies to seven out of Koch's 47 cases[21] and to several of Hermann's,[20] even without unconsciousness, as in four out of Proctor's[29] 32 cases. Correspondingly, Wittmaack[36] found total atrophy of the left organ of Corti in a 30-year-old woman who had been hit, at the age of 14 years, behind the left ear by a stone-hard snowball. She developed pain, vertigo, and hearing loss, but not unconsciousness, bleeding or discharge from the ear.

Re 2. In the present series there are seven cases of concussion or 5.7%. By way of comparison, it may be mentioned that perusal of health cards for 200 normal pupils (20 from each of ten grades, aged seven to 16 years) showed that 8 or 4% had been admitted to hospital with concussion.

Re 3. The frequency of head injuries on the whole, before and after deafness was detected, was 12 and nine respectively. The frequency of injuries involving concussion was three and four respectively.

Head injuries are discussed so thoroughly, although no fracture had occurred, because evidently moderate injury may give rise to unilateral total deafness. Thus, it cannot be ruled out with certainty that a few cases of head injuries in young children, apart from the one described above, may have been responsible for the deafness. Since,

TABLE IV

OBJECTIVE FINDINGS AND ETIOLOGY

			VESTIBULAR FINDINGS REACTION			X-RAY FINDINGS INNER-EAR CAVITIES	
			NORMAL	ABSENT	ABNORMAL	ABNORMAL	
Congenital 101	Without demonstrable hereditary basis	74	57(77%)	16(22%)	1(1%)	11(15%)	15%
	With hereditary basis	27	19(70%)	8(30%)	25%	4(15%)	
Acquired 20*	Meningitis	11	3(27%)	8(73%)	77%	5(45%)	56%
	Labyrinthitis (otogenic)	2	0	2		2	
	Mumps	5	5		50%		35%
	Sudden idiopathic deafness	1	1				
	Scarlet fever	1	1				

* One case of head injury not included.

however, the frequency of concussion in this series is, on the whole, like that in the control series and since the frequency and severity of the head injuries within the entire series are the same for cases occurring before and after detection of the deafness, there is no decisive indication that any case, apart from the one already mentioned, was due to head injury.

Accordingly, the acquired causes of unilateral deafness may be summarized as in Table III.

As already mentioned, endogenous factors appear to have been operative in 30 families. In three of them, there were, in addition, exogenous factors in explanation of the deafness in the subject (Families I, II, XVI). If 27 cases are attributed to endogenous and 21 to exogenous factors, the etiology was demonstrable in 48 cases or 39.9%.

The clinical-etiological study of unilateral deafness was based partly on a thorough history and partly on a number of objective investigations.

In connection with the clinical and etiological features, there arises the question whether the objective examination of the subject at hand can in any way contribute to elucidating the etiology or merely to classifying the cases as congenital or acquired.

It was mentioned in previous publications[17,18] and touched upon in some of the present case histories that vestibular function studies and x-ray examination showed certain abnormalities which are tentatively classified by etiology in Table IV. Abnormal vestibular function will be seen in 25% of the congenital and in 50% of the acquired cases, whereas abnormal x-ray findings were observed in 15% and 35% respectively. The abnormalities were particularly common in the groups of meningitis and labyrinthitis. Although the named morbid changes are encountered mainly in acquired cases, their relatively high frequency in the congenital group indicate that, regrettably, vestibular and x-ray studies cannot be of decisive differential diagnostic value, lacking an explanation in the history.

As far as vestibular studies are concerned, Lindenov[26] and Arnvig[7] arrived at the same conclusion in studying persons with total deafness and severe hardness of hearing.

As to the x-ray appearances, Uffenorde,[34] examining 101 deaf-mutes, found a differentiated labyrinthine pattern in all 46 inherited

cases, whereas 18 out of 55 acquired cases, or 33%, showed a more or less marked blurring of the labyrinthine lumen.

In 11 patients (9%) of the present series, whose personal and family history was negative, the x-ray appearances revealed that the lesion was due to developmental anomalies.[17]

Thus, in about 50% the etiology was not demonstrable.

SUMMARY

The etiology of unilateral total deafness in children and young adults was thoroughly studied clinically, radiologically, and genetically in a series of 122 individuals. The clinical findings have been reported in a previous paper.

Hereditary factors were demonstrable in about 25%, consisting in the occurrence of all degrees of severity of endogenous perceptive lesions, but mainly severe ones, in the families studied, and by a predisposition to acquired deafness in a few families.

The transmission was by irregular dominant inheritance.

In 21 instances (17%), the disease appeared to be acquired, due to meningitis in 11 cases, mumps in five cases, otogenic labyrinthitis in two, scarlet fever in one, and head injury in one. Lastly, one case occurred as sudden idiopathic deafness.

Prenatal, natal and neonatal causes could not be demonstrated.

In 9% the x-ray appearances revealed that the lesion was due to developmental anomalies.

In about 50% the etiology was not demonstrable.

Brief mention is made of the relationship between vestibular findings and x-ray appearances of the inner ear on the one hand and etiology on the other. Abnormal findings were made in this respect in 50% and 35% respectively in the acquired group and in 25% and 15% respectively in the congenital group.

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REFERENCES

1. Albrecht, W.: Arch. Ohren- Nasen- u. Kehlkopfh. 110:15, 1923.
2. Albrecht, W.: Ztschr. f. Laryng., Rhin., Otol.14:1, 1926.
3. Albrecht, W.: Ztschr. f. Hals- Nasen- u. Ohrenh. 29:18, 1931.
4. Albrecht, W.: Ztschr. f. Hals- Nasen- u. Ohrenh. 34:261, 1933.
5. Anderson, N., Brown, E., and Lyon, R.: Am. J. Dis. Child. 65:523, 1943.
6. Arnvig, J.: Proceedings of the International Course in Paedo-audiology, Groningen University, 1953.
7. Arnvig, J.: Acta Oto-laryng. 45:283, 1955.
8. Arnvig, J.: Acta Genetica et Statistica Medica 9:41, 1959.
9. Bentzen, O., and Jelnes, K.: Acta Oto-laryng. 45:189, 1955.
10. Bierman, Th. A.: Sudden Perceptive Deafness. Dissertation, Leiden, 1957.
11. Birkholz, H.: in: Denker, A., u. Kahler, O.: Handb. der Hals- Nasen- Ohr enheilk. 6:795, 1926.
12. Everberg, G.: Acta Oto-laryng. 45,198, 1955.
13. Everberg, G.: Acta Oto-laryng. 47:303, 1957a.
14. Everberg, G.: Acta Oto-laryng. 48:397, 1957b.
15. Everberg, G.: Acta Psychiat. et Neurol. Scand. 32:307, 1957c.
16. Everberg, G.: Acta Oto-laryng., in press, 1960a.
17. Everberg, G.: Acta Oto-Laryng., in press, 1960b.
18. Everberg, G.: Acta Oto-laryng., in press, 1960c.
19. Fisch, L. J. Laryng. and Otol. 73:355, 1959.
20. Hermann, R.: HNO., 5:166, 1955.
21. Johnson, S., and Freiesleben, E.: Acta Oto-laryng. 42:35, 1952.
22. Kemp, T.: Genetics and Disease, Copenhagen, 1951.
23. Kinney, C.: Laryngoscope 63:220., 1953.
24. Koch, J.: Arch. Ohren- Nasen- u. Kehlkopfh. 137:105, 1933.
25. Kristensen, H. K.: Acta Oto-laryng. 36:66, 1948.
26. Lindenov, H.: The Etiology of Deaf-mutism. Copenhagen, 1945.
27. Marschak, A.: Ztschr. f. Laryng., Rhin., Otol. 21:145, 1931.
28. Medicinalberetning for Kongeriget Danmark, 1957, I. Kobenhavn, 1959, p. 108.
29. Proctor, B., Gurdjan, E., and Webster, J.: Laryngoscope 66:17, 1956.
30. Schneider, K.: Ztschr. f. Hals- Nasen- u. Ohrenh. 42:314, 1937.
31. Smith, A.: Lancet 237:1172, 1939.
32. Toynbee, J.: Diseases of the Ear. London, 1860.

33. Trolle, E.: Acta Psychiat. et Neurol. Scand. Suppl. 66, 1951.

34. Uffenorde, H.: Hals- Nasen- u. Ohrenarzt, 1. Teil, 30:88, 1939.

35. Waardenburg, P.: Am. J. Human Genet. 3:195, 1951.

36. Wittmaack, K.: Arch. Ohren- Nasen- u. Kehlkopfh. 131:59, 1932.

37. Vogelsang, Reich and Barth: Erbbl. Hals- Nasen- u. Ohrenarzt 28:35, 1937.

38. World Health Organization: Expert Group on Prematurity. Technical Report Series nr. 27. Geneva, 1950, p. 4.

39. Zange, J.: Pathologische Anatomie und Physiologie der mitterohrentspringenden Labyrinthentzündungen . . . , Wiesbaden.

LIV

PSYCHIC FACTORS IN HEARING LOSS

JANE C. FARLEY, PH.D. WILLIAM W. WALDROP, M.S.
A. J. DERBYSHIRE, PH.D. RICHARD L. CARTER, PH.D.
DAVID F. AUSTIN, M.D. CLARENCE MCCORMICK, B.A.
AND PETER J. MILLS, M.S.
CHICAGO, ILL.

The study described here should be looked at as a reconnaisance operation, a preliminary exploration of a new conception of the nature of hearing and hearing loss. This new view is proposed, so that we may integrate the whole domain of psychological factors with the acoustic and physiological and clinical-medical factors which are conventionally set forth as the totality of hearing. The propriety of including psychological data should be fairly obvious, since "hearing" and "deafness" (or hearing loss) are words which refer to the psychological realm of personal experience.

The vocabulary of physics and acoustics can discuss the characteristics of stimuli, and the vocabulary of physiology can discuss perceptual-receptor phenomena, neural transmission, and cortical activity, but neither physics nor physiology properly deals with the essentially subjective data of hearing or failing to hear. Medical clinicians discuss in more global terms the anatomic, physiologic, and behavioral pathology associated with various forms of hearing losses, but must invoke psychological laws whenever they trace the implications of clinical performance, as reflecting particular degrees of auditory awareness.

Our research is aimed at more meaningful and testable definitions of psychic factors in hearing loss. We attempt to outline the psychic events which may predispose, cause or contribute to hearing losses, and to identify with as much precision as possible the locus and the nature of psychic interferences in the hearing of these seven pilot subjects. The results of tests on seven subjects, however intensively

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studied, cannot be offered as scientific conclusions. Rather, the results given here will be used as working-hypotheses to be more painstakingly validated in a larger population of patients with defective hearing.

Primarily, we think of our study as a research model containing crucial revisions of some of the central concepts in the field of hearing, a set of theoretical propositions which relate our concepts, and a battery of tests which are our operational definitions for these concepts and statements-of-relationship. In this pilot study, our research design, the definitions, and the procedures used are tried out experimentally, in a miniature but authentic "baptism by fire."

THE BASIC CONCEPTS

Literature on psychic hearing loss has tended often to obscure, rather than to clarify the parasomatic* role of the psyche. The psychic functions are either loosely incorporated, and thereafter ignored (as presented in some of the articles on "functional" hearing loss), or a contrast is emphasized between the organic and the psychic factors (in an equal body of literature on "non-organic" hearing loss). Actually, neither approach adequately represents all of the described events. The former method (non-specific recognition of psychic events into a concept of functionality) confounds—and ultimately submerges altogether—the part which the psyche plays. The latter view (separation of organic and psychic) violates a wholistic appraisal of the individual, as an indivisible psychophysiological individual.

We know that the psyche is itself an animistic name for a group of complex neuronal activities. We can conveniently put the same label on this whole group of processes, because of their common characteristic of proximity to observable behavior, and because they are in many ways more closely related to one another than they are to other neurologic systems. By this grouping of psychic activities, we have been able to develop some of the laws which govern psychologic expression, without first locating the processes anatomically. This artificial partitioning has fostered the growth of a psychologic science, but the convention of psychic/organic dualism has also created obstacles to the understanding of functions which involve the coordinated action of the entire individual. For the sake of a lawful and scientific psychological model, we will erect this partition our-

* This is a neologism—since we know of no coined phrases which represent the psychic-somatic relationship as a parallel one, in which the same phenomenon can be artificially separated into two alternative ways of viewing, like the two faces of a single coin.

selves, and speak of a psychological model, of psychic effects operating on physiological processes, etc. But we will implicitly bear in mind the actual organic unity of the psycho-physiological human subject; and we will recognize this unity by limiting our hypotheses to those which are both psychologically and physiologically plausible. That is, we will not offer as a hypothesis any psychological model, however internally consistent, which leads to physiological absurdity, and vice versa. Further, wherever possible, we will include in our definitions of psychic processes any substantial clues we may have as to the anatomic loci or physiological mechanisms which underlie them.

But it is not enough simply to avoid these theoretical pitfalls, and to mark them with caution signs. Embarrassments about where to put psychology in the hearing act have also created a number of troublesome detours. The attempts to submerge or to isolate psychic factors in hearing and deafness show up in many of the popular clinical assumptions in this area. The most ubiquitous single oversimplification which results from the submergence of psychic factors is the popular clinical assumption that standard audiometric thresholds are measurements of hearing. What in fact is measured by standard audiometry is a certain kind of behavioral performance, from which, in the context of particular kinds of acoustical phenomena, the quantity of experienced hearing is inferred. If this seems both an obvious and a hair-splitting distinction, bear with us. In the framework we are about to propose, it has considerable importance and meaning.

An equally popular oversimplification can be traced to the attempts to isolate and contrast psychological and organic factors. This is the notion that malingering is the only important form of psychic interference in hearing. This assumption implies that psychic activity can only be expressed in conscious, voluntary ways—i.e., that the psyche is related to behavior, but not to the behaving organism. It is our belief that the conscious, voluntary behavior of a subject is merely the terminal point in a complex, sequential process which begins with the acoustically definable stimulus and ends with the visible, gross response (e.g., in the testing situation, tapping a key or raising a finger).

Our approach to the hearing problem involves seven basic definitions, and, one central assumption. The first four of these definitions represent in general our medico-physiological framework.

1. *Hearing*: is the series of events which begins with the impingement of any sound stimulus on the tympanum, and ends with the

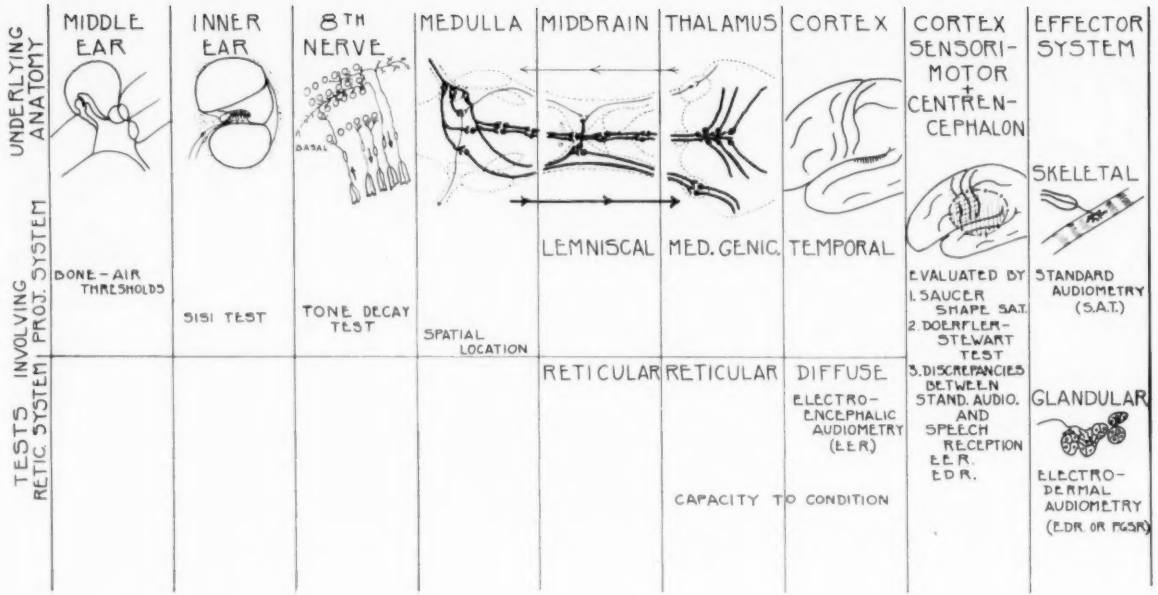

Fig. 1.—A schematic representation of hearing, from stimulation to response. The anatomic points in the sequence are shown in relation to the tests which are used to assess functioning at each of these points.

subject's meaningful response to that stimulus; together with the anatomic loci and physiologic functions which participate in this series of events.

2. *Hearing Loss*: is a loss of auditory information at any point (or points) in the hearing sequence.

3. *Auditory Information*: is defined operationally as the correlation between the auditory stimulus (acoustically-initiated energy) which reaches a given point in the series (the input to that point), and the response to that stimulus (output of the point), inferred from what is transmitted to the next subsequent point.

4. *Points in the Hearing Sequence*: We conceive the physiological hearing sequence to be roughly as follows:

Middle ear to sense organ (cochlea), via the VIII nerve to the medulla (medullary cochlear nuclei, superior olive, etc.), thence to the midbrain (inferior colliculus). From the midbrain to the temporal lobe by two concomitant pathways:

1) Midbrain to thalamus (medial geniculate) to temporal lobe.

2) Midbrain (region of the inferior colliculus) through reticular systems to temporal lobe.

And finally from temporal lobe through cortico-thalamic paths to sensori-motor cortex and to final output systems.

(Figure 1 is a schematic representation of these major phases or points in the hearing act, plus the tests and measurements we use as operational definitions of these points.)

When we speak of deaf (or hard-of-hearing) people, we include everyone who loses auditory information at any point, and in consequence, acts as if deaf.[10] Included are people whose audiograms show hearing deficit, but the definition is not limited to that group alone. We also consider deaf (or hard-of-hearing) anyone who so defines himself, whether audiometric data support his self-definition or not.

The points in the sequence are used to distinguish different classes of hearing loss. Using this general framework, we can cluster various types of hearing impairment by reference to the point of principal loss. For example, an otosclerotic patient is one in whom the middle

ear is the point of greatest loss. At the other end of the sequence, a malingerer is a subject whose locus of primary loss is somewhere between the sensori-motor cortex, which frames a response, and the skeletal muscle effectors used e.g. in pushing down the key in audiometric testing.

The remaining three basic definitions are psychological, and require a shift in the frame of reference which the reader is asked to assume. They represent the three fundamental psychic conditions for hypothesizing psychic interference in the hearing act.

1. *Availability*:* Psychic availability of the symptom refers to the existence in the life history of the person, of a model for the experience of deafness or the behavior of deafness, such that the person is able to recall (or imitate) either the subjective feelings of hearing deficit, or the outward appearance of hearing deficit (i.e., either the experience or the behavior of deafness must be available in the subject's subjective or expressive repertoire).

2. *Necessity*: The psychic necessity for the symptom refers to the existence in the person of designatable conflicts, which cannot be resolved in any more economical way,* and which can be resolved uniquely by this auditory loss.

3. *Maintenance*: Psychic maintenance refers to the current gains and gratifications which the person receives from the symptom, and which balance its cost, to him, in participation and communication with his environment.

The one central assumption, which we ask the reader to make with us, deals with the interaction of psychic and physiological factors in producing hearing losses. It is this:

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* Availability remains the least well-defined factor, either in terms of psychic theory or of neurophysiological mechanisms. We have, however, some clinical evidence of the occurrence and some clues as to the possible psychodynamics of such learned psychic modifications (as altered perceptual functions), through an investigation of another learned psychic modification—*folie a deux*—which has been demonstrated to be transmitted through close interpersonal interaction.[9]

* We accept here (as indeed elsewhere) the general psychoanalytic viewpoint, which tells us, among other things, that a psychodynamic solution to a problem tends to be as efficient as possible, granting the individual's interpretation of the problem, and within the limits of the alternative solutions possible for that individual, i.e., psychodynamic solutions do not waste psychic energy.

Both psychic and organic factors contribute to every instance of hearing loss. We feel justified in making this assumption, since it can be demonstrated that in the strictest sense, every person (normal or hearing-handicapped) displays both organic hearing loss and psychic hearing loss constantly. All of us have some organic auditory deficit, since the hearing mechanism does not transmit all of the sounds which are physically present, as anyone who has ever summoned a pet with a high frequency whistle can attest. It is equally true, though perhaps not as obviously so, that we are all psychically deaf from time-to-time, since we all selectively perceive (become deaf to all but a small number of available stimuli) in moments of concentration, or even of daydreaming. It has also been demonstrated experimentally that the behavior of normal subjects can be modified by sound stimuli appreciably below the level of conscious awareness. Rationally also, the assumption of a psychic and an organic face for every state of an individual becomes necessary if we say (as we have done) that that individual is a psycho-physiological unity.[5]

THE MODEL FOR PSYCHO-PHYSIOLOGICAL INTERACTION IN THE ETIOLOGY OF HEARING LOSSES

Granting that organic and psychic factors always combine in producing a hearing loss (acting-as-if-deaf), we can express the possible derivations of hearing losses logically as shown in Figure 2.

We can then translate these logical possibilities into four general clinical classifications. Each of these clinical groups, of course, must be describable in terms of known physiologic mechanisms, which might underlie each category, as well as in terms of logical or psychological possibility.

The four clinical groups (represented in Figure 2) are:

1. *Psychic Hearing Loss*: The so-called pure hysterical deafness in which the role of organic deficit is minimal, existing only as a model for the experience of deafness. Here, the origin and target of the loss are both located within higher brain centers, between which communication is constant and for which no special mechanisms need be designated.

2. *Psychogenic (Psychosomatic) Hearing Loss*: Cases in which an originally intact auditory sequence is eventually damaged by neuronal processes which have a psychic origin. To justify the inclusion of this clinical class, we must designate mechanisms by which the psyche

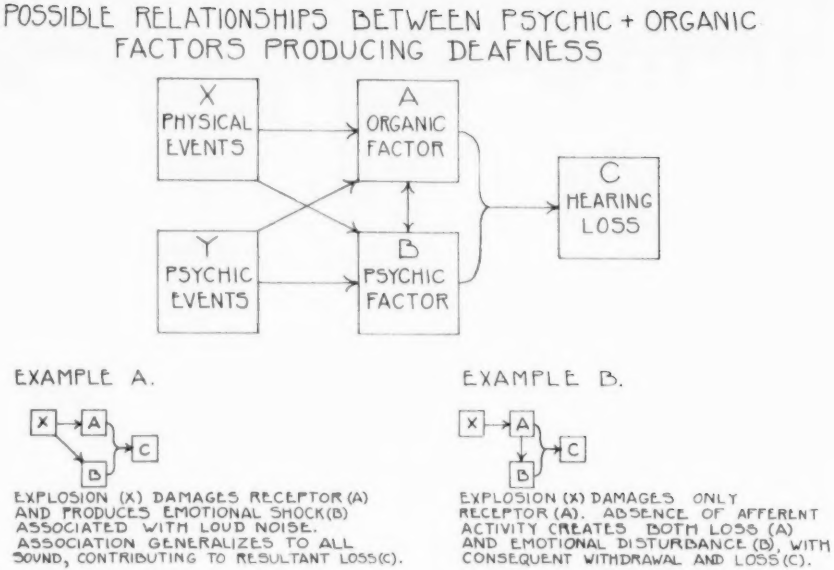


Fig. 2.—Schema showing the possible causal sequences, leading to the combination of organic (A) and psychic (B) factors necessary for producing a hearing loss (C). Either organic or psychic factors—or both—may be hereditary, or cause may be unknown; or either or both types of factors may be produced by physical or psychic events. Examples of two causal sequences stemming from the same physical event illustrate the use of the model.

might act to influence organic points in the hearing sequence which are earlier in the sequence than those usually thought of in connection with psychic functions. We feel that current descriptions of the efferent auditory pathways[2,8,13] have outlined anatomically and neurophysiologically the routes that might be taken by impulses from the cortex (which could conceivably be psychic in origin) to produce blocking at earlier stages. Notably, the mapping of the efferent olivocochlear bundle[8] allows us to consider the possibility of psychic interference as early in the segment as the cochlea. (Indirect psychic effects (i.e. psychic factors—modifications of the internal milieu—changes in operation of auditory system) are also possible. Neurotic anxiety (e.g.) differs from objective anxiety principally in its object. The physiologic reaction pattern (ortho-sympathetic activation) is virtually the same. Diffuse chemical changes can in turn influence any part of the hearing sequence—e.g. through changes in fluid-consistency reflected in impedance changes in labyrinthine fluid.[6,14])

3. *Functional Overlay*: Cases in which an organic impairment of whatever origin, sets up a psychic reaction which enhances the impairment. In this case, as in the hysterical hearing loss, the multiplicity of cortical neuronal connections suffices as a neuronal substrate for this kind of psychic interference.

4. *Conscious Malingering*: Cases in which the behavior of the person is influenced by psychic processes, some of which are conscious. Organic deficit exists only as a model for the behavior of deafness.

Clearly these clinical groupings overlap, when applied to particular cases, but such a system of classification may serve as a basis for differentiating clusters of individual cases which have a similar etiology and course.

THE RESEARCH DESIGN

A. *The Population.* The patients used in this preliminary study were selected (as the larger population will be also) from persons referred to the Speech and Hearing Service, Presbyterian-St. Luke's Hospital, Chicago, Illinois. Since we hoped to uncover psychic factors in deafness, we selected those patients with an already-suggested primary psychic component, feeling that they would be more likely to generate testable hypotheses than a group in whom psychic interference was more subtle. These patients are representative of particular patients whose hearing losses show substantial psychic components, and we cannot meaningfully extend our results to apply to hearing

CLINICAL GROUPINGS DERIVED FROM CAUSAL MODEL

CLINICAL CLASSIFICATION	PSYCHIC	PSYCHOGENIC (PSYCHOSOMATIC)	FUNCTIONAL OVERLAY	MALINGERING
	(A_L) Y→B } → C	A ↑ B } → C	A ↓ B } → C	(A_D) Y→B } → C
TARGET	THE PSYCHE SYMBOLIC AND/OR INTEGRATIVE FUNCTION	THE BODY PHYSIOLOGIC AUDITORY PATHS	THE PSYCHE SYMBOLIC AND/OR INTEGRATIVE FUNCTION	THE BEHAVIOR
ORIGIN	THE PSYCHE	THE PSYCHE	THE BODY PHYSIOLOGIC AUDITORY DEFICIT	THE PSYCHE AND EXTERNAL MOTIVATING FACTORS
EXPERIENCE	NO SOUND OR "CANNOT UNDERSTAND" THE SOUNDS	LESSENED OR DISTORTED AUDITORY SENSATIONS	REDUCED OR ABSENT SOUND OR "CANNOT UNDERSTAND"	UNWILLINGNESS TO ADMIT HEARING, OR REFUSAL TO LISTEN
POSSIBLE MECHANISM	HIGHER CENTERS ACT ON THEMSELVES OR RECEPTION AREA	HIGHER CENTERS ACT ON SENSE ORGAN + AFFERENT PATH THRU AUDITORY EFFERENTS	DECREASE OF AFFERENT IMPULSES ACTING ON HIGHER CENTERS	HIGHER CENTERS ACT ON EFFECTOR AREA OF HIGHER CENTERS

Fig. 3.—A clinical classification of the types of hearing loss, developed from the causal model, and differentiated on the basis of the origin and target (points in the hearing sequence) of the loss; the subjective experience of the person suffering the loss, and the possible mechanism(s) by which the loss is effected.

losses in general, although we hope to do just that in the final phase of our research (expected date of completion, 1963).

Except for the condition of suggested psychic loss, we tried to vary the population sample as much as possible; and our group covers a wide range of age and social class, with equal representation (approximately) of both sexes.

B. *The Procedures.* Each patient was hospitalized, and subjected to a battery of examinations and tests, representing as comprehensive a view as possible of his total functions (organic and psychic). Tests in each field were selected by an expert in that field (fields covered: otology, neurology, internal medicine, psychiatry, social service, audiology, and psychology). Tests were made and interpreted by each of the experts (otologist, neurologist, internist, etc.) independent of all data except that of his own field, as gathered under his direction.

After the individual interpretations had been made, the group met, as a team, to discuss their separate diagnostic summaries. The findings of each team member were listed on a summary sheet, which represented the hearing act, in terms of the various points or stages. A sample summary sheet, with specific reference to the data from which it was compounded, is given in the appendix.

C. *Validation of the Interpretive Analyses.* We recognize that the only conclusive validation of a diagnostic analysis is in the results of a therapy program based on that diagnosis. It is thus our belief that we can only demonstrate the specific causal statements contained in our hypotheses by such a comparison. We must first integrate psychological and organic findings into a total etiologic-prognostic picture; then design therapy programs individually to fit each of the complex diagnostic statements. The subjects' responses to these therapies are the only validating criteria for the specific psychodynamic hypotheses. However, we felt that we could confirm or repudiate the potency of psychologic factors in producing the final hearing loss by comparing independent judgments of this factor, within the research design. That is to say, the content of the independently derived psychological diagnostic hypotheses (specific conflicts and life situations, etc.) can only be validated by the course and the results of psychotherapy; but the psychologically-derived estimate of the relative importance of psychic factors in the hearing loss can be validated by comparison with a more objectively-based estimate of psychological contributions to the loss.

EVALUATION OF PSYCHIC COMPONENTS OF HEARING LOSS

AUDIOMETRIC INDEX	PSYCHOLOGIC INDEX
1. Z = SPEECH RECEPTION – STANDARD AUDIOMETRIC THRESHOLDS (SRT – SAT) $Z = \frac{\frac{1}{2}(SRT-SAT)_{BE} + (SRT-SAT)_{FF}}{2}$	1. N = NECESSITY (STRONG CONFLICTS) IN TERMS OF DEFENSIVE ENERGY UNRESOLVED CONFLICTS FELT-DISCOMFORT
2. Y = DIFFERENCE BETWEEN SAT. AND CORRESPONDING POINT ON STRAIGHT LINE CONNECTING HIGH AND LOW FREQUENCY THRESHOLDS (A) $Y = \frac{\frac{1}{2}\Sigma(SAT - A)_{BE}}{N-2}$	2. I = IRREALITY (LOOSENING OF REALITY TIES)
3. X = DOERFLER–STEWART TEST $X = SRT + 20 - N_0$ N_0 = NOISE NECESSARY TO MASK INTELLIGIBLE SPEECH	3. M = MAINTENENCE (GAINS OFFERED BY SYMPTOM) IN TERMS OF NEED SATISFACTION AND AVOIDANCE OF NEGATIVE SITUATIONS
4. W = DIFFERENCE BETWEEN SAT AND ELECTRODERMAL THRESHOLDS (EDR) $W = \frac{\Sigma(SAT - EDR)}{N}$	(IN THE PRESENCE OF)
5. V = DIFFERENCE BETWEEN SAT AND ELECTROENCEPHALIC THRESHOLD (EER) $V = \frac{\Sigma(SAT - EER)}{N}$	4. A = AVAILABILITY THE EXISTENCE IN THE HISTORY MATERIAL OF A CLEAR MODEL FOR THE EXPERIENCE OR THE BEHAVIOR OF DEAFNESS
$\frac{V+W+X+Y+Z}{5} = \Psi_i$ CORRELATED WITH	$\Psi_c = N+I+M(+A)$

Fig. 4.—Defines the "scores" which make up the comparable audiometric and psychologic indices of "psychogenicity."

TABLE I

PSYCHOLOGIC/AUDIOMETRIC ESTIMATES OF PSYCHIC INVOLVEMENT

Correlation Between the Audiometric Index of Psychogenicity (Ψ_1) and the Psychologic Measures of: Necessity (Psychol. 1), Loosening of Reality Ties (Psychol. 2), Maintenance (Psych. 3), (including all possible pairings of these scores), and the Full Psychologic Index ("Total").

	PSYCH* 1	PSYCH* 2	PSYCH* 2	1 & 2	1 & 3	2 & 3	TOTAL	SPEECH FREQ.	LOW FREQ.	TOTAL**	SP. & LOW
Psych 1		0.587	0.671	0.899	0.889	0.707	0.861	0.798	0.762	0.811	0.825
Psych 2			0.607	0.888	0.654	0.863	0.828	0.137	0.463	0.336	0.317
Psych 3				0.718	0.937	0.926	0.903	0.516	0.598	0.564	0.589
1 & 2					0.867	0.880	0.948	0.529	0.689	0.646	0.644
1 & 3						0.908	0.966	0.697	0.731	0.733	0.755
2 & 3							0.969	0.394	0.601	0.519	0.526
Total								0.564	0.701	0.659	0.669
Sp. f.									0.790	0.937	0.946
Low f.										0.940	0.946
Total											0.993
Sp. & Low											

*Psych-1 refers to the group of indices which bear on psychic necessity: Defensive operations, unresolved conflicts, discomfort, and decompensation.

*Psych-2 refers to the group of indices which express loosening of reality ties: i.e. irreality, immunity from reality demands, and unrewardingness of reality.

*Psych-3 refers to the Maintenance factors—those which select and maintain perceptual impairment specifically as the primary adjustive mechanism: i.e. self-injury, succorance needs, consistent self-concept, removal of temptation and distraction, and direct evidence of perceptual blocking.

**The audiometric designations are self explanatory, except for the "total," which includes high frequency data in those five subjects for whom high-frequency thresholds were taken.

Specifically, the objective measurement used as a validation-criterion for the psychological diagnosis was an "index of psychogenicity" yielded by the various audiometric measurements. This was then correlated with a psychological index of psychogenicity, based on scoring of psychological material, interpreted in accordance with the "necessity, maintenance, availability" framework, with an additional factor (loosening of reality ties) added. Figure 4 summarizes the components of the two comparable indices.

The correlation of these two independently derived measurements (audiometric/psychologic) of the proportion of psychic factors in the etiology and current functioning of a hearing loss constitutes the primary validation of our psychodynamic hypotheses, in this pilot study. Table I is a statistical table, showing the amount of agreement between these specific psychologic and audiometric estimates of psychic involvement. The upper right-hand corner (marked off in -------) expresses the particular correlations which are of interest, in confirming our hypotheses. The over-all agreement of psychological and audiometric estimates is +0.659. (We have underlined also all of the individual correlations which were +0.6 or above. These correlations of +0.6 or above cover more than half of the comparisons measured. If we choose the more equal, but less cautious, significance point of +0.5 or over, 83% of the pairings will be considered significant.) Although confidence limits were not computed (with 7 subjects—or six degrees of freedom—the computing of confidence levels would be a meaningless pretension), a correlation of +0.6 or above constitutes clear support of our basic hypotheses.

SUMMARY

A pilot study illustrates the design, and suggests working hypotheses for a research aimed at specifying the psychic factors which may predispose, cause, or contribute to inefficiency in the use of (organically) available auditory information, at any point in the hearing act. The hearing act is here defined as the sequence of events beginning with the impingement of the stimulus on the tympanum—and ending with the subject's meaningful response to that stimulus.

Definitions, and theories relating those definitions, are offered, and a rationale and procedure for the testing of these theoretical formulations is demonstrated on a preliminary group of seven patients, in whom a substantial psychic component has been suspected. These subjects were intensively studied by medical, audiometric, psychologic, and social investigations, during a week of hospitalization.

Findings are independently evaluated, so that cross-correlations between them might be used in confirming hypotheses.

In view of the preliminary nature of this study, no intensive analysis of results is given. The central psychodynamic hypotheses are validated by comparison with more objective, and independent, estimates of psychogenicity, and the results show strong enough support for these hypotheses to warrant more extended study. Primarily, however, the research is offered as a model for research into multiply-caused defects in hearing (and possibly other whole-person disorders as well). We feel that the concepts and definitions of the various events in the hearing act, as presented here, provide points of contact between the traditionally (and artificially) separated approaches of psychically, oriented investigators, and those whose primary area of interest is somatic and neurological; i.e., the theoretical model herein proposed can be operationally defined in medical and psychological terms simultaneously. Psychic hypotheses are restricted to those for which neural mechanisms can be demonstrated, and somatic and neural hypotheses are similarly limited to those which do not violate psychic function.

The tested hypotheses concerning the psychic availability, necessity, and maintenance of auditory loss, as an adjustive mechanism, are in general supported by independently analyzed audiometric indicators of psychogenicity.

ILLINOIS INSTITUTE OF TECHNOLOGY

REFERENCES

1. Brain and Human Behavior: Association for Research in Nervous and Mental Diseases. Baltimore: William and Wilkins, 1958.

2. Bocca, E.: Notes on Innervation of the Cochlear. A.M.A. Arch. Otolaryng. 55:188-205, 1952.

3. Davis, H.: Transmission and Transduction in the Cochlea. The Laryngoscope 68:359-382 (Mar.) 1958.

4. Derbyshire, A. J., and Farley, Jane: Sampling Auditory Responses at the Cortical Level. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 68:675-697, 1959.

5. Derbyshire, A. J., and Groen, J. J.: The Auditory Response. Proposed presentation at International Acoust. Soc. Meetings, Stuttgart, Germany.

6. Doerfler, L. G.: Psychogenic Deafness and Its Detection. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 60:1045 (Dec.) 1951.

7. Fulton, J. F.: Physiology of the Nervous System. (3rd ed.) New York: Oxford Univ. Press, 1949.

8. Galambos, R.: Neural Mechanisms of Audition. Physiol. Rev. 34:497-528, 1954.

9. Gralnick, A.: Folie a deux—the Psychosis of Association; a Review of 103 Cases and the Entire English Literature, with Case Presentations. Psychiat. Quart. 16:230-263, 1942.

10. Hardy, W. G., and Pauls, Miriam D.: The Test Situation of PGSR Audiometry. J. Speech and Hear. Disord. 17(1):13-24 (Mar.) 1952.

11. Henry Ford Hospital: International Symposium on Reticular Formation of the Brain. Boston: Little, Brown, 1958.

12. Henry, W. E.: The Analysis of Fantasy. New York: Wiley, 1956.

13. Rasmussen, G. L.: Further Observations of the Efferent Cochlear Bundle. J. Comp. Neurol. 99:61-74, 1953.

14. Weille, F. L., et al.: An Experimental Study of the Dynamic Circulation of the Labyrinthine Fluids of Living Mammals. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 68:733-739, 1959.

15. Withrow, F. B., Jr., and Goldstein, R.: An Electrophysiologic Procedure for Determination of Auditory Threshold in Children. Laryngoscope 1674-1699, 1958.

LV

VESTIBULAR RESPONSES OF SOME DEAF AND APHASIC CHILDREN

BENJAMIN ROSENBLÜT, M.D.
ROBERT GOLDSTEIN, PH.D.
AND
WILLIAM M. LANDAU, M.D.
ST. LOUIS, MO.

The vestibular responses of a population of deaf and aphasic children at Central Institute for the Deaf were studied as part of a more inclusive neurologic assessment.[7,11] Other vestibular studies have been reported in deaf children[4,5,8,12] and in some aphasic children.[13] The present investigation is unique because the population was large and because the children were also studied carefully from many related aspects.

MATERIAL AND METHODS

The subjects were 164 children in full time classes at Central Institute for the Deaf. Of these, 107, 65.2%, were classified as deaf, and 57, 34.8%, were classified as aphasic. The classification of each child was made by the school principal and supervisors on the basis of clinical data and educational progress. Sixteen normal children of similar age were also examined to provide a basis of comparison.

Vestibular function was tested by a modification of the test originated by Fitzgerald and Hallpike.[6] Instead of water at 30°C and 44°C, a stronger stimulus, 18°C, was used because our original purpose was to screen those children who gave no vestibular responses. After the ear canal was cleaned, the chilled water was injected against the tympanic membrane for 40 seconds (average volume about 330 cc).

From the Central Institute for the Deaf, and the Division of Neurology and Electroencephalography, and the Beaumont-May Institute of Neurology, Washington University School of Medicine, St. Louis, Missouri.

This study was partially supported by Grant B-240 from the National Institute of Neurological Diseases and Blindness.

The tests were performed in a semi-darkened room with the subject's eyes illuminated by reflected light from a head mirror. The children were instructed to stare straight ahead but no fixation point was given. One observer (B.R.) judged the amplitude and frequency of nystagmic movements, and the moment when all nystagmic movements ceased. Subjective reactions were noted, but, because of difficulties in communication, they were often difficult to interpret and were not considered in the evaluation of responses.

Duration of nystagmus was measured from the moment water began to flow into the ear canal until all visible nystagmic movements ceased. The amplitude of movement was judged on a four point scale: the largest responses were designated by "4", the smallest by "2", and no response by "1". Frequency of nystagmus was similarly designated: "4" for the highest frequency, "2" for the lowest, and "1" for no response.

RESULTS

Normal. These children ranged in age from 3 years, 7 months to 13 years, 6 months. No differences were found related to sex or age, and therefore, all 16 are treated together in Table I. (In these calculations each of the 32 durations, 2 for each child, is treated as an independent measure.) The mean and median duration of nystagmus to the closest 5 seconds was 145 sec. (Standard deviation $= \pm 14.31$ sec.) The shortest duration was 120 sec.; the longest, 175 sec. Table I also shows the relation between duration and both amplitude and frequency, and the almost identical responses of both ears in the same person.[9]

All these subjects had reactions of dizziness, and some became nauseated.

Deaf and Aphasic Children. A similar tabulation to that of Table I was made for the deaf and aphasic children. Inspection of the data and calculations of correlation coefficients indicated that in this population also there were close relations among duration, amplitude and frequency, and between responses from the two ears. Therefore, an arbitrary measure of vestibular function, the duration of nystagmus in the left ear, was chosen.

Vestibular responses were then placed in one of three categories. The first was no response at all. The second category, depressed response, included those lasting 115 seconds or less. This value is shorter

TABLE I

VESTIBULAR RESPONSES OF NORMAL CHILDREN*

SUBJECT	SEX	AGE yr. mo.	DURATION OF NYSTAGMUS (in seconds)	AMPLITUDE	FREQUENCY	DURATION OF NYSTAGMUS (in seconds)	AMPLITUDE	FREQUENCY
1	F	9 - 11	130	3	4	140	3	4
2	F	9 - 5	135	3	4	135	3	4
3	F	6 - 9	130	2	3	130	2	2
4	F	11 - 7	160	3	4	165	4	4
5	F	7 - 10	175	3	3	175	3	3
6	F	10 - 1	160	3	4	150	3	4
7	F	11 - 7	135	3	3	125	3	2
8	F	13 - 0	125	3	3	120	3	3
9	M	3 - 7	160	3	4	150	3	3
10	M	5 - 6	145	3	2	140	3	3
11	M	10 - 7	135	3	2	140	4	3
12	M	13 - 6	155	3	4	160	3	4
13	M	12 - 5	140	3	4	165	3	4
14	M	9 - 9	145	3	4	160	3	4
15	M	6 - 7	150	2	3	145	2	2
16	M	5 - 11	145	3	4	155	3	4

* See text for details.

than any recorded for the normal children, and is at least two standard deviations from the mean of the normals. Durations of 120 seconds or more were classified as normal.

1. *Relation to Educational Classification* (Table II). The principal findings here are a) that more than half of the deaf children, 51.4%, but only 36.8% of the aphasic children gave normal vestibular responses, and b) that proportionately there were many aphasic children, 43.9%, but few deaf children, 23.4%, who showed depressed vestibular responses.

Meningitis and associated severe infections are known to damage the VIII nerve in many instances. Table IIB excludes children with histories of such illnesses. Now there is proportionately a still greater prevalence of normal responses among the deaf, 56.8%, than among the aphasic children, 38.2%.

TABLE II

VESTIBULAR RESPONSES OF DEAF AND APHASIC CHILDREN

	A. Total Population				*B. Restricted Population**			
	DEAF		APHASIC		DEAF		APHASIC	
	N	%	N	%	N	%	N	%
Normal	55	51.4	21	36.8	50	56.8	21	38.2
Depressed	25	23.4	25	43.9	24	27.2	25	45.5
No response	27	25.2	11	19.3	14	15.9	9	16.3

*Excluding children with history of meningitis or other severe infantile infection.

TABLE III

ETIOLOGIC CLASSIFICATION

		DEAF	APHASIC
A.	Meningitis Severe infection in infancy Family history of hearing loss	32	5
B.	Maternal rubella Complication during pregnancy	19	11
C.	RH Complication of labor and birth Convulsive disorder Congenital brain abnormality Family history of speech or neurologic disorder	3	27

2. *Relation to Etiologic Factors.* Various pre-, peri-, and postnatal etiologies could be determined with considerable certainty for 97 of the children. The etiologic categories were grouped into three classifications which are shown in Table III, slightly modified from an earlier report.[7] These etiologic groupings were developed to separate the deaf from the aphasic children as clearly as possible. The distribution of vestibular responsiveness (Table IV) is clearly related to etiological factors ($X^2 = 16.08$ $p < 0.01$).

The biggest deviation from chance expectation derives from the disproportionately great number of children in category A who showed no vestibular responses. This category includes meningitis and other

TABLE IV

VESTIBULAR RESPONSES AS A FUNCTION OF ETIOLOGIC CLASSIFICATION

VESTIBULAR RESPONSE	ETIOLOGIC CATEGORY* A	B	C
Normal	12	16	11
Depressed	5	11	9
Absent	17	1	4

* Cf. Table III.

severe infections in infancy, and family history of hearing loss, conditions in which the VIII nerve structures are presumably affected. Moreover, only one child in category B had absent vestibular responses, and only five in category A had depressed responses. Thus with a history of category A there are usually normal vestibular responses or none at all.

3. *Relation to Hearing Level.* The audiograms were placed in one of the three categories. Group I contains flat and U-shaped audiograms. Group II contains the sloping audiograms with relatively good sensitivity for the low frequencies and with responses to high frequencies at least to 2000 cps. Group III contains the "residual" type audiograms with no responses above 1000 cps. The average hearing level was best in Group I, and poorest in Group III.

Eight children whose hearing level was normal and three whose measured hearing levels were unreliable are not included in the following calculations. Of the eight with normal hearing, four showed normal responses and two showed depressed responses. Two others had been tested with 10 cc of ice water in a preliminary study; one gave normal responses, the other gave none.

Vestibular and auditory functions (Table VI) are not independent ($X^2 = 13.05$, $p < 0.05$),[8] i.e., the greater the auditory impairment, the greater the vestibular impairment. The group finding, however, is difficult to apply diagnostically to individuals because all combinations can occur. At the extremes, 16.1% of the children with relatively good auditory sensitivity gave no vestibular responses and 43.3% of the children with poorest sensitivity gave normal responses.

TABLE V

VESTIBULAR RESPONSES AS A FUNCTION OF MAJOR MOTOR ABNORMALITIES

VESTIBULAR RESPONSES	NORMAL	MAJOR MOTOR ABNORMALITY
Normal	70	6
Depressed	45	4
Absent	33	6

TABLE VI

VESTIBULAR RESPONSES AS A FUNCTION OF AUDIOMETRIC PATTERNS

VESTIBULAR RESPONSE	AUDIOMETRIC PATTERNS* I	II	III
Normal	18	27	23
Depressed	8	30	10
Absent	5	9	19

* See Text.

4. *Relation to Major Motor Abnormality.* Vestibular responsiveness seems to be independent of the major neurologic abnormalities found in a relatively small group of children.[11]

5. *Relation to EEG.* Comparison of vestibular responsiveness to the EEG findings failed to show any dependent relations (Table VIIA). This was true also when focal and non-focal EEG abnormalities were compared with vestibular function. None of the 13 children, however, with abnormal EEGs and no vestibular responses had a focal EEG pattern[11] (Table VIIB).

COMMENT

The principal finding in this study is the greater proportion of abnormal responses among aphasic than among deaf children. In both populations, however, there are many children with responses of all

TABLE VII A

VESTIBULAR RESPONSES AS A FUNCTION OF EEG NORMALITY

VESTIBULAR RESPONSES	ELECTROENCEPHALOGRAM	
	NORMAL	ABNORMAL
Normal	45	30
Depressed	28	22
Absent	25	30

TABLE VII B

VESTIBULAR RESPONSES AS A FUNCTION OF FOCALIZATION OF EEG ABNORMALITIES

VESTIBULAR RESPONSES	EEG ABNORMALITIES	
	NON-FOCAL	FOCAL
Normal	20	10
Depressed	15	7
Absent	13	0

degrees. This indicates that vestibular tests have negligible value in the differential diagnosis of auditory disorders in young children. As others have observed[4,5,8] the presence of normal responses does not rule out deafness. The absence or depression of responses could be related to severe labyrinthine or peripheral neural impairment or to presumed lesions of the central nervous system as in aphasic children.

In adults, directional preponderance[1,3,6,10] (not studied here) and irregularities in nystagmus[2,14] have been noted with various CNS lesions, usually unilateral ones. The mechanism of the poor responses in our aphasic children is not clear but we do assume that they have some CNS impairment and that the impairment is bilateral.

Vestibular responsiveness seems more clearly related to etiologic factors than to any other studied. We have previously noted[7] that etiologic data were also more predictive of the diagnosis of deafness or aphasia than any of five other factors studied.

SUMMARY

Vestibular responses to caloric stimulation at 18°C were tested in 107 deaf and 57 aphasic children. Duration of nystagmus was measured from the beginning of flow of water into the ear canal. On the basis of the responses of 16 normal children a duration of 120 seconds or more was considered normal. Responses were classified as absent, depressed (115 sec duration or less), and normal.

A recent study of vestibular function in schizophrenic children[15] showed a degree of vestibular hypoactivity similar to that observed in our aphasic children. Of the 43 schizophrenic children studied "23 were currently non-verbal." We believe that the aphasic and schizophrenic categories may present overlapping diagnostic difficulties.

As a group the aphasic children showed poorer vestibular responses than did the deaf children. Vestibular responsiveness in the total population was more clearly related to etiology than to any other factors.

There was a significant relation between the depression of hearing sensitivity and the depression of vestibular responsiveness, but not enough to be predictive for the individual case.

JEWISH HOSPITAL OF ST. LOUIS

REFERENCES

1. Anderson, H. C., and Kristiansen, F.: Directional Preponderance of Caloric Nystagmus in Aphasia. Acta Psychiatrica et Neurologica Scandinavica, Suppl. 108: 23-27, 1956.

2. Anderson, P. J., Diamond, S. P., Bergman, P. S., and Nathanson, M.: Electro-oculographic Investigation of the Caloric Response. Neurology 8:741-749, 1958.

3. Carmichael, E. A., Dix, M. R., and Hallpike, C. S.: Lesions of the Cerebral Hemispheres and Their Effects Upon Optokinetic and Caloric Nystagmus. Brain 77: 345-372, 1954.

4. Carruthers, D. G.: Congenital Deaf-Mutism as a Sequela of a Rubella-Like Maternal Infection During Pregnancy. Medical Journal of Australia 32:Part I:315-320, 1945.

5. Christoph, C. H.: Occurrence of Congenital Family Deaf-Mutism in Six Children. A.M.A. Archives of Otolaryngology 38:300-302, 1943.

6. Fitzgerald, G., and Hallpike, C. S.: Studies in Human Vestibular Function. I. Observations on Directional Preponderance ("Nystagmusbereitschaft") of Caloric Nystagmus Resulting from Cerebral Lesions. Brain 65:115-137, 1942.

7. Goldstein, R., Landau, W. M., and Kleffner, F. R.: Neurologic Assessment of Some Deaf and Aphasic Children. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:468-479, 1958.

8. Guilder, R. P., and Hopkins, L. A.: Auditory Function Studies in an Unselected Group of Pupils at the Clarke School for the Deaf. III. Relation Between Hearing Acuity and Vestibular Function. Laryngoscope 46:190-197, 1936.

9. Hallpike, C. S., Harrison, M. J., and Slater, E.: Abnormalities of the Caloric Test Results in Certain Varieties of Mental Disorder. Acta Otolaryngologica 39: 151-159, 1951.

10. Kirstein, L., and Preber, L.: Directional Preponderance of Caloric Nystagmus in Patients with Organic Brain Diseases. Acta Otolaryngologica 44:265-273, 1954.

11. Goldstein, Landau, Kleffner: Neurologic Observations in a Population of Deaf and Aphasic Children. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY (in press).

12. Langova, J., and Siroky, A.: Poruchy vyvoje detske rece ve vztahu K funci vestibularniho ustroje a poloze plodu. CSL. Otolaryng. 6:287-295, 1957 (abstracted in Excerpta Medica, Section XI, 11:186, 1958).

13. Mitrinowincz-Modrzejewska, A.: Vestibular-Chronaxie und ihre Bedeutung für die Untersuchung des taubstummen Kindes. Archiv Ohren-usw. Heilk. u. Z. Hals-usw. Heilk. 172:175-179, 1957.

14. Riesco-MacClure, J. S., and Stroud, M. H.: Dysrhythmia in the Post-Caloric Nystagmus. In preparation.

15. Colbert, E. G., Koegler, R. R., and Markham, C. H.: Vestibular Dysfunction in Childhood Schizophrenia. A.M.A. Archives of General Psychiatry 1:600-617, 1959.

LVI

NEUROLOGIC OBSERVATIONS ON A POPULATION OF DEAF AND APHASIC CHILDREN

ROBERT GOLDSTEIN, PH.D.
WILLIAM M. LANDAU, M.D.
FRANK R. KLEFFNER, PH.D.
ST. LOUIS, MO.

The diagnostic delineation of the child whose speech and communication are disturbed is seldom easy, even in the presumably simple case of deafness in which the peripheral auditory apparatus is damaged. Since the pathogenesis of aphasia in children is even less well understood, the empirical criteria leading toward diagnosis are often insecure. Of course, both deafness and aphasia must often be distinguished clinically from mentally retarded and psychotic conditions, but the latter diagnostic groups will not be considered further here.

It was anticipated that neurologic evaluation, particularly of aphasic children, might support the view that aphasia is due to dysfunction of the central nervous system (CNS). The aphasic children in full-time classes at Central Institute for the Deaf were studied because this group offered the diagnostic advantage of several years of observation of their progress in a specific educational program.[7] The deaf children in the school were also studied in order to determine possible differential diagnostic criteria, and the incidence of signs of neurologic deficiency among them. The final educational diagnosis of aphasia or deafness by the teaching staff was used as the major criterion by which the present data are classified.

The measurement of vestibular function in these children is described in the following paper.[8] A preliminary report of both studies has been published.[4]

From the Central Institute for the Deaf, and the Division of Neurology and Electroencephalography and Beaumont-May Institute of Neurology, Washington University School of Medicine, St. Louis, Missouri.

This study was partially supported by Grant B-240 from the National Institute of Neurological Diseases and Blindness.

MATERIAL AND METHODS

All of the 188 children in the school over a two year period were included in the study. Five children tentatively considered aphasic were later reclassified as neither aphasic nor deaf and were excluded from the final evaluation. Of the remaining 183, 69 were diagnosed as aphasic and 114 as deaf. The aphasic group was not uniform; one half had moderately severe hearing losses and six had borderline mental retardation in repeated tests. Nevertheless all were included because the aphasic difficulty seemed to be the major handicap. Ages at the time of the study ranged from 4 to 14 years.

In all cases a narrative history was obtained from the parents on one or more occasions, and in most cases a standard questionnaire was filled out at the interview. In a few cases the questionnaire was mailed to the parents, and additional information, when needed, was obtained by correspondence. Necessary additional data from other physicians and hospitals were also secured.

As complete a neurologic examination as possible was done in each case and was repeated when necessary. With instructions by gesture, confrontation visual fields and double simultaneous touch stimulation were almost always accomplished successfully, and motor tests were readily imitated. A standard waking EEG, including hyperventilation whenever possible, was performed on 182 subjects, and skull x-rays were obtained on 157. Several children had previously had pneumoencephalograms, all normal, in other centers. Serial audiometric and psychometric test data were available for all children.

RESULTS

Neurologic Examination. Twenty children were found to have some significant defect of motor function such as abnormalities of gait and tone, extensor plantar responses, choreoathetosis, or severely inept co-ordinated movements. Of these, 16 (23.2%) were aphasic, and only 4 (3.5%) were classified as deaf ($p < 0.001$).

A variety of minor findings were not significantly related to the major abnormalities, or to the educational classification of deaf or aphasic. Thus, concomitant strabismus was seen in 3 of the aphasic children and in 8 of the deaf. Nystagmus on lateral gaze (sustained but usually fine) was seen in 2 aphasic and 4 deaf subjects. Miscellaneous findings such as chorioretinitis, unequal pupils, ptosis of an eyelid, etc., were noted in 16 children: 6 aphasic and 10 deaf.

Double simultaneous stimulation of face and hand was successfully perceived by most children. Two in each group failed to perceive the hand stimulus after 8-10 trials, although they did understand the test. Some children in both groups could not be taught the appropriate response for the test (see below).

Ewing[3] observed that deaf children often scrape their feet along the floor in walking, presumably because they are unaware of the noise they produce, whereas aphasic children lift their feet normally. We found that this was not a helpful sign in our population because foot slurring was observed in 55% of the deaf, and in 56% of the aphasic children. (Many aphasic children also have significant impairment of auditory sensitivity.)

A test of rhythmic movement consisted of having the subject imitate the examiner's patting of the subject's thighs in bursts of three equally spaced strokes, followed by a pause with the hands raised, and then repetition of the three pats, etc. Each subject was given at least three demonstrations and tests if needed. Slightly more than 72% of both groups of children were unable to duplicate the rhythm, although they clearly understood the test. (Several older children, both deaf and aphasic, who succeeded counted the beats out loud.) Rhythmic sensorimotor performance is thus affected in some children with either type of auditory disorder.

Handedness was determined by preference in writing, catching and throwing. Eyedness was tested by having the subject imitate the examiner as he sighted through a short length of pipe, holding the pipe in each hand in separate tests.

Among the 114 deaf children, 97 were right-handed, and of these, 59 were right-eyed, 31 left-eyed, and 7 indeterminate. Of the 14 left-handed deaf children, 8 were left-eyed, 5 right-eyed, and 1 indeterminate. In 3, handedness was not consistent. Of the 69 aphasic subjects, 60 were right-handed, 25 were also right-eyed, 21 left-eyed and right-handed, and 14 had indeterminate eyedness with dextrality. The 8 left-handed aphasic children included 4 with left-eyedness, 3 with right-eyedness, and 1 with indeterminate eyedness. Handedness was indeterminate in 1 aphasic child. Thus neither handedness, eyedness, nor their dissociation are related significantly to the educational diagnosis, or, so far as we can determine, to pathogenesis.

Electroencephalograms. Routine bipolar waking recordings were made in 182 children. In a few the eyes remained open, and in some,

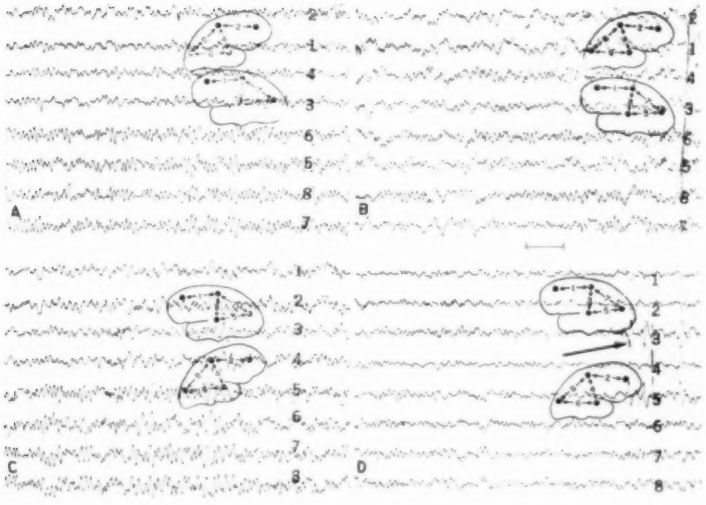


Fig. 1.—Sample EEGs from the seven-year age group. A. Normal (deaf). B. Normal "tension" record (aphasic). C. Diffuse slow record (aphasic). D. Left temporal spike discharge, see arrow (aphasic).

successful hyperventilation was not accomplished. The records were evaluated independently by two electroencephalographers (WML and JLOL); one was familiar with some of the cases, and the other was told only the child's age. Differences of interpretation were few, related only to degree of slow activity for age, and were invariably resolved in the conservative (normal) direction. Records that did not show focal discharge were originally grouped as dysrhythmic, borderline or "tension" record, and normal. Subsequently in the following analysis, both the latter groups were considered within normal limits (Fig. 1).

Forty, 58%, of the 69 aphasic children had normal records. Of the remainder, 4 had left temporal spiking; 1, bitemporal spiking; 1 left occipital slow focus; 4 bioccipital slow activity; and 19, diffuse slow activity. By comparison, 70, (62%), of the 113 deaf children also had normal records. Two had left temporal spikes, 5 had bioccipital slow waves, and 36 were diffusely slow. Thus about 40% of each group had dysrhythmic EEGs, an incidence hardly to be expected among the children presumed to have only peripheral auditory lesions.

More focal abnormalities were observed in the records of the aphasic (14.5%) than of the deaf (6.1%).

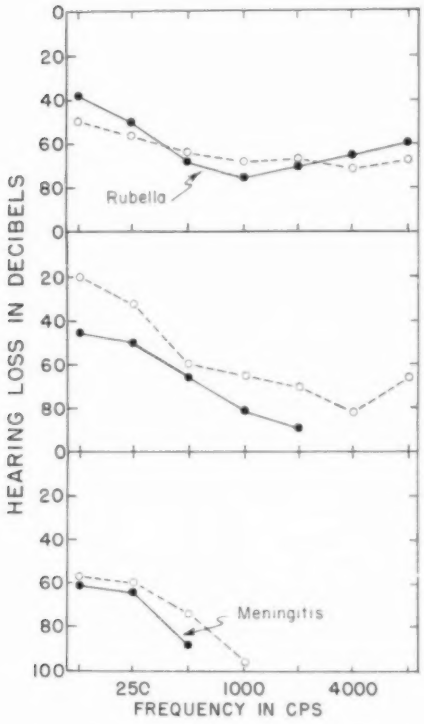
Skull X-rays. Examinations were made in 157 subjects. Chronic mastoiditis was reported in one deaf and two aphasic children. Parietal asymmetry was seen in two, and occipital flattening of the cranial vault in two others, all aphasic. Thus a CNS developmental anomaly is suggested in a small group of aphasic subjects.

Vestibular Function. These findings are related in detail in the following paper.[8] As a group the aphasic children showed *poorer* responses than the deaf.

Obtuseness. By this term we mean that some children, though generally co-operative and not apparently disturbed, were nevertheless frustratingly slow at abstracting or "getting the idea" of several aspects (non-verbal) of the examination. The majority of both deaf and aphasic children, most of whom had minimal speech perception (even through speechreading), were surprisingly apt at learning the "game" of the examination by gestural demonstration and imitation. For example, the child was required to nod or vocalize when a target was presented in the peripheral visual field; he had to touch one or two points on the body surface which were first touched by the examiner; he had to walk on his toes and on his heels in imitation of the examiner. Obtuseness was difficult to quantify except by the reaction of the examiner and the duration of the examination. Of 18 children where such behavior was noted, 2 were classified as deaf (1.8%) and 16, aphasic (23.2%).

This phenomenon may relate to general intelligence since the mean test scores for the obtuse children (89.2, Randall's Island Test; 96.4, Advanced Performance Test) were lower than those in the whole population (see below). Still, 5 had scores on the Advanced Performance Test of more than 100 (one 128), and another scored 123 on the Randall's Island Test. Thus obtuseness, which doubtless parallels the behavior called aphasic by the educational staff, can occur in children who do well on a standardized intelligence scale.

Psychometry. One hundred and eighty one of the children took either the Randall's Island or the Advanced Performance Tests, the former usually being administered to the younger children.[1,6] Many had both tests, but if either test was repeated the initial score was used for the following statistics. Among the deaf children (71 tested of 114) the mean Randall's Island score was 115.5 (S.D. 14.82); the



[2] Fig. 2.—Each of the six curves represents the 50th percentile of the distributions of audiograms with similar configurations, but with varying degrees of hearing loss. In each of the three sections approximately an equal number of children are represented in each of the two curves. Aphasic children are predominantly represented in the upper section (flat and U-shaped audiograms), and the deaf, in the lower section ("residual" audiograms of varying severity). Deaf and aphasic are approximately equally represented in the intermediate group of sloping audiograms. (See text.)

mean score for the aphasic group (30 tested of 69) was 102.8 (S.D. 16.64). The deaf children (100 tested of 114) also did better on the Advanced Performance Test, 121.8 (S.D. 22.36); the aphasic group (58 tested of 69) scoring a mean of 104.0 (S.D. 18.18). Similar significant differences in larger groups were shown by Bilger,[2] but he was unable to show any differentiating subtests in the Advanced Performance Test. Whether the lower scores of the aphasic children are due to a perceptive difficulty has not been determined. In any case

the difference in intelligence test scores for the two groups is too small to be of practical utility in individual diagnosis.

Audiometry. Satisfactory threshold audiograms were determined for 173 of the children.[9] Nine of the aphasic children had essentially normal thresholds. Audiograms of the remaining 164 can be classified in one of three major categories (Fig. 2). These are: flat and U-shaped audiograms with an average level in the speech range of 60-70 db; sloping audiograms with responses at least to 2000 cps (many showing better hearing at 8000 cps than at 4000 cps); and sloping audiograms with no response above 1000 cps. The average hearing levels of the flat and U-shaped audiograms (upper section of Fig. 2) are about equal. The two audiograms of the sloping type (intermediate section) differ primarily in severity. The same is true for the two "residual" audiograms in the lower section. For each section approximately an equal number of children are represented in each of the two curves.

A greater proportion of the aphasic than of the deaf children had the flat and U-shaped audiograms (21 aphasic, 13 deaf). The U-shaped audiogram is characteristic of most children whose difficulty is traced to maternal rubella. There were approximately equal proportions (43 deaf, 32 aphasic) in the intermediate category. In the last group of essentially "residual" audiograms, 54 of the 55 children were deaf. The majority of those children who gave no responses to frequencies above 500 cps, had histories of meningitis or other severe infantile infection.

Of course, the aphasic children as a group showed far greater auditory sensitivity than the deaf children. Nevertheless, the presence of a serious hearing loss does not preclude aphasia in the same child.

Etiology. Except for a few cases with major motor abnormalities which were assumed to relate to prenatal factors even when there was no history of specific disturbance, all conclusions were based upon retrospective historic data (Table I). Arbitrary rules for each category proved difficult to apply; a cause was assigned only when we considered that the total information about a case would be convincing to most clinicians. Unconfirmed vague recollections of parents were not relied upon; a measure of our skepticism is that 47% of the cases were considered to be of unknown etiology.

For example, hereditary deafness was considered only when there was definite knowledge of congenital deafness in near relatives; late acquired deafness was disregarded. Similarly, multiple cases of famil-

TABLE I

ETIOLOGIC CLASSIFICATION OF DEAF AND APHASIC CHILDREN (see text)

	DEAF	APHASIC
UNKNOWN	60	26
PRENATAL		
Heredity		
1. Hearing loss	12	3
2. Speech disorder, CNS disorder	0	6
Rubella in first trimester of pregnancy	10	7
Other congenital complications		
1. Historical data	9	4
2. Inferred from clinical evidence of brain damage	2	5
Rh, severe jaundice shortly after birth	0	4
PERINATAL		
Complications of labor and birth	1	6
POSTNATAL		
Meningitis	9	1
Severe infection in infancy	11	1
Convulsive disorder	0	6

ial congenital CNS disturbances, a related disorder in a sibling, or familial history of retarded speech development beyond the age of 4 led to another hereditary classification. The significance of threatened abortion was measured by the symptom history, the obstetric management, and the nature of the termination of pregnancy. Similar precautions were used for evaluation of each etiologic class.

The category of severe infantile infection is illustrated by a child who developed epidemic enteritis on the third day of life. She had a high fever and dehydration, and was treated for several weeks with streptomycin and other antibiotics. Three other infants affected in the same epidemic had succumbed.

The convulsive-disorder group includes two children who became aphasic after apparently normal development of speech.[5] Four other

children had infrequent recurrent seizures associated with retarded speech development and no other apparently significant etiologic factor. We considered that the latter group is of the same type, differing only in the age of onset of speech disturbance. Recurrent seizures were reported in no other children, deaf or aphasic, although five in each group had had single seizures, five associated with meningitis, and five with other acute illnesses.

A regrouping of etiologic data which tends to segregate the deaf and aphasic is presented in Table II. Thus, Group A includes a signif-

TABLE II

CONDENSED REVISION OF ETIOLOGIC CLASSIFICATION
(see text)

		DEAF	APHASIC
A	Meningitis Severe infection in infancy Family history of hearing loss	32	5
B	Maternal rubella Complication during pregnancy	19	11
C	Rh Complication of labor and birth Convulsive disorder Congenital brain abnormality Family history of speech or Neurologic disorder	3	27

icant predominance of deaf children, Group C, of aphasic, and Group B, approximately the same proportion of both.

Miscellaneous Data. A two to one predominance of males was found in both deaf and aphasic groups. Of the deaf, 74 were boys and 40 girls, and there were 46 boys and 23 girls in the aphasic group.

Head banging (or rhythmic movements) was reported in 26 deaf and 22 aphasic children, and thus offers no discriminative value. Inconstant behavioral response to environmental sounds such as airplanes, sirens, and loud noises was reported in many aphasic but in no deaf children. (Such responses, even if inconstant, are one criterion for the diagnosis of aphasia.) Both deaf and aphasic children

TABLE III

SUMMARY OF DIAGNOSTIC DATA FOR DISTINGUISHING DEAF AND APHASIC CHILDREN

	Most Useful						Least Useful
	ETIOLOGY	HEARING	MOTOR SYSTEM	VESTIBULAR SYSTEM	EEG	SKULL X-RAYS	PSYCHOMETRY
	meningitis	sloping audiogram	no major abnormality	normal, except for children with meningitis, etc.	normal or dysrhythmic	normal	higher range normal
Deaf	severe infantile infection						
	family history of hearing loss						
Deaf or Aphasic	maternal rubella	sloping audiogram	no major abnormality	normal, depressed or no response (with sloping audiogram and moderately severe hearing loss)	normal or dysrhythmic	normal	normal
	RH complication of labor and birth	normal hearing, or flat audiogram with moderate hearing loss	major abnormality	depressed (with normal hearing or moderate hearing loss)	focal abnormality	anomaly of cranial vault	lower range normal
Aphasic	convulsive disorder						
	congenital brain abnormality						
	family history of speech or neurologic disorder						

usually liked television, but the deaf were seldom aware of the audio portion.

The parents of aphasic children were much less often aware of the child's perceptive difficulty for sound in the first two years of life. The deaf children's parents usually reported consistent unresponsiveness to sound.

COMMENT

Although it has been presumed that some CNS dysfunction accounts for the clinical phenomena of congenital aphasia, 22 (32%) of the aphasic children had no additional abnormalities in any of the neurologic studies performed. Moreover, the minor physical findings (14.5%), and the dysrhythmic EEGs (42%), were no more common among the aphasic than among the deaf population.

Thus only gross neurologic abnormalities and a few etiologic categories are effective additional indicators of the aphasic category. Nevertheless the auditory and speech behavior and the educational progress of the "neurologically normal" third of the aphasic children could not be distinguished in any way from that of the remainder. We can only presume on the basis of clinical similarities that all have pathophysiologic features in common.

A summary of all of our diagnostic criteria is presented in Table III.

SUMMARY

A neurologic study was carried out upon 183 children in a school for the deaf and aphasic. The tests included medical history, neurologic examination, EEG, skull x-rays, audiometric studies, psychometric tests and vestibular function tests. Where available, etiologic factors were also correlated with clinical and laboratory findings. The general findings are summarized in Table III.

JEWISH HOSPITAL

REFERENCES

1. Bilger, R. C.: Limitations on the Use of Intelligence Scales to Estimate the Mental Ages of Children. Volta Review 60:321-325, 1958.

2. Bilger, R. C.: Personal Communication. 1958.

3. Ewing, A. W. G.: Aphasia in Children. London, Oxford University Press, 1930.

4. Goldstein, R., Landau, W. M., and Kleffner, F. R.: Neurologic Assessment of Some Deaf and Aphasic Children. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:468-479, 1958.

5. Landau, W. M., and Kleffner, F. R.: Syndrome of Acquired Aphasia with Convulsive Disorder in Children. Neurology 7:523-530, 1957.

6. Lane, H. S., and Schneider, J. L.: Performance Test for School-age Deaf Children. American Annals of the Deaf 86:441-447, 1941.

7. McGinnis, M. A., Kleffner, F. R., and Goldstein, R.: Teaching Aphasic Children. Volta Review 58:239-244, 1956.

8. Rosenblüt, B., Goldstein, R., and Landau, W. M.: Vestibular Responses of Some Deaf and Aphasic Children. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, this issue.

9. Smith, E. K.: Relation of Audiometric Patterns to the Etiology of Auditory Disorders in Children. Master's Thesis, Washington University, 1957.

The Scientific Papers of the American Laryngological Association

(Continued)

LVII

CINEFLUOROGRAPHY IN THE PRE- AND POST-OPERATIVE MANAGEMENT OF LARYNGEAL CANCER

JOHN A. KIRCHNER, M.D.
JAMES H. SCATLIFF, M.D.
DONALD P. SHEDD, M.D.
NEW HAVEN, CONN.

Partial laryngectomy or well planned irradiation may control or cure cancer in locations where laryngectomy would involve unnecessary sacrifice of function. The possibility of carrying out function-sparing surgery or irradiation in any particular case depends upon the meticulous study of the tumor's size, inferior extent and invasion of neighboring tissues. This information frequently cannot be drawn from endoscopic examination alone, because of the distortion, fixation, bleeding, pain and anesthesia problems often produced by introduction of the laryngoscope. Much of this information, however, can be obtained from roentgenograms or laminograms of the larynx and hypopharynx,[1-5] particularly after coating them with a radiopaque material as described briefly by Farinas in 1942[6] and as illustrated and documented by Powers in 1957.[7]

Motion, however, is a particularly important feature of a neoplasm and its bed, since it reflects the degree of spread into neighbor-

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From the Divisions of Otolaryngology, Radiology and General Surgery, Yale-New Haven Medical Center.

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ing tissues. This can be studied by fluoroscopy,[8] and recorded by instruments like the Fairchild rapid changer.[9] This instrument produces 9x9-inch roentgenograms of good detail, but since its maximum output is two pictures per second, it seems too slow to compare with cinefluorography in demonstrating the rapid movements of the larynx and pharynx.

Cinefluorography dates almost from the time of the discovery of x-rays, but it was not until the availability of x-ray image intensifiers in 1953 that the techniques assumed a useful place in roentgen diagnosis. The history of its development and the various methods of carrying out the procedure are clearly described in a well-illustrated article by Tristan.[10]

Its application to the pharynx and larynx has consisted chiefly of recording normal deglutition, using barium mixtures.[11]

About three years ago, we began to use cinefluorography in our clinic to study dysphagia in patients recovering from laryngectomy (see report of cases). Next, we began using it to study motion and fixation in tumors under consideration for radiation therapy, and have found it so useful that it now forms a routine part of the investigation of every laryngeal or hypopharyngeal malignancy. The motion picture helps indicate the tumor's size, extent and degree of invasion, particularly in areas difficult to visualize endoscopically.

An even more interesting application of this technique is the postoperative investigation of such complications as cough, regurgitation, dysphagia, or recurrent neoplasm (see report of cases). From an investigative standpoint it affords a means of correlating esophageal voice with various modifications of laryngectomy or laryngopharyngectomy.

The examination consists of motion-picture fluoroscopy recording of a barium mixture as it passes through the pharynx on swallow. A Philip's five inch amplifier, 16 mm Auricon camera and linograph ortho film are used. The larynx is then locally anesthetized, oily Dionosil is instilled and a fluoroscopic motion-picture recorded during phonation, inspiration and Valsalva maneuver.

After development, the film is shown by a 16 mm projector equipped with a device which allows slow motion, complete stop or

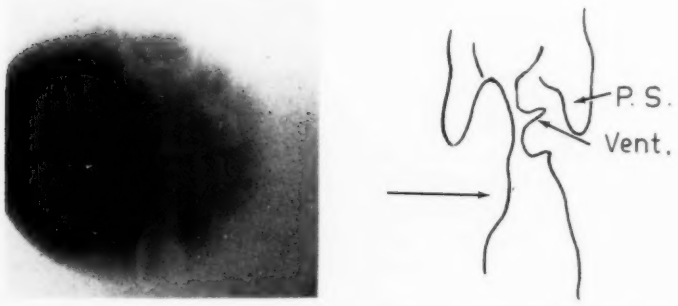

Fig. 1.—16 mm frame showing indentation of right tracheal wall by tumor mass, with fixation (lower arrow). Pyriform sinuses (P.S.) fill normally, left ventricle fills normally, but the right is occluded by tumor and does not fill with Dionosil.

reversal of direction. In this way the laryngologist can study the tumor as often as necessary, and at his leisure.

REPORT OF CASES

CASE 1. V.R., a 73 year old white male admitted with irregular fungating mass over the anterior two-thirds of the right vocal

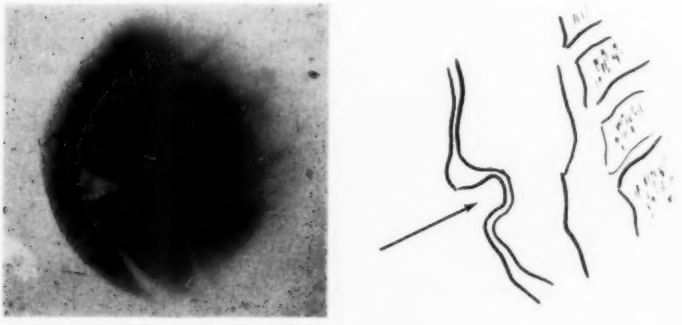

Fig. 2.—16 mm frame showing tumor involvement of anterior commissure with fixation (arrow) and with normal subglottic area.

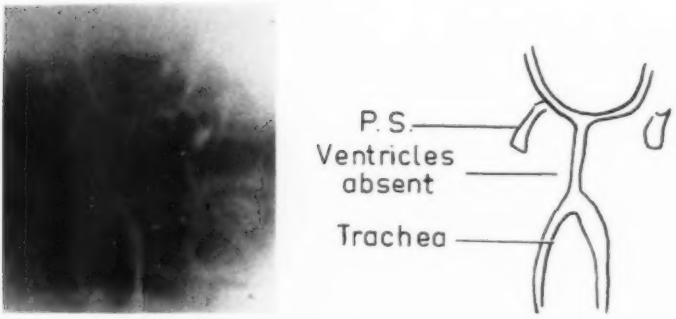

Fig. 3.—16 mm frame showing complete absence of ventricular filling in bilateral ventricular cancer with movable vocal cords and subglottic tissues.

cord. It appeared to originate from the ventricle, extend forward into the anterior commissure and downward into the subglottic area, although its extent could not be definitely determined. Left cord partially fixed. The false cord normal. Biopsy—epidermoid carcinoma.

Laminograms were reported as of poor quality but suggestive of subglottic edema.

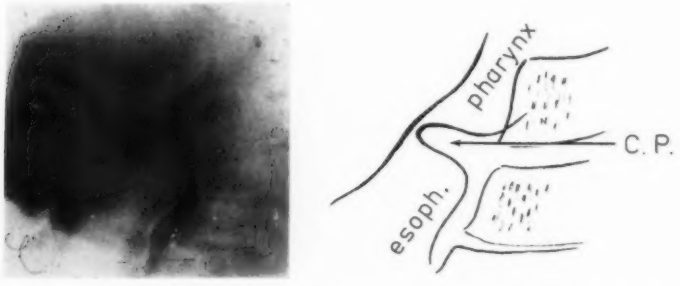

Fig. 4.—16 mm frame showing flattening and change in shape of the mass seen in Figure 4. When viewed in the motion picture, the mass resembles muscle, with good motion.

Fig. 5.—Roentgenogram of post-laryngectomy muscle mass suggesting recurrent neoplasm.

Cinefluorograms showed fixation of the right true cord, absence of the right ventricle and a prominence and fixation of the wall of the subglottic area (Fig. 1).

Total laryngectomy carried out with uneventful recovery.

Comment. This lesion was difficult to visualize endoscopically, particularly the portion in the ventricle and the submucosal portion in the subglottic area. Laminography was reported as suggesting edema, while cinefluorography showed definite fixation of the swollen area, indicating neoplasm and not edema. While laminography often shows the size and extent of a tumor, as well as its lower limits, the success of the technique varies with the patient's ability to co-operate and to sustain phonation, not only for a single, but for repeated sections. The procedure is often difficult for both the patient and the examiner. Lateral laminograms often fail in short necked, heavy patients who cannot be positioned satisfactorily.

Cinefluorography in this case helped corroborate the clinical impression of fixation of the cord and demonstrated the submucosal extension of the tumor in its entirety.

By contrast, in the case of V.F., a small subglottic carcinoma showed excellent motion on cinefluorography. Radiation was carried out with excellent results and no evidence of tumor at present, 18 months after radiation.

CASE 2. G.V., a 64 year old white man. Laryngoscopy was complicated by bleeding from a large neoplasm involving the anterior two-thirds of the right vocal cord, with fixation. The anterior commissure could not be well seen. Tracheotomy performed. Biopsy of right vocal cord—epidermoid carcinoma. Lower edge of tumor could not be identified.

Cinefluorography showed involvement of the anterior commissure, movable cords, and a clear subglottic area (Fig .2).

Radiation was carried out with excellent control to date.

Comment. In this case the lower edge of the tumor was very difficult to identify because of bleeding, pain, fragmentation of tissue, etc. Cinefluorography showed the outline of the tumor quite well

Fig. 6.—Postoperative out-pouching of pharynx which frequently develops where the upper end of pharyngeal suture line meets the base of the tongue.

and showed that the subglottic area was free of tumor and that there was no anterior extension into the pre-epiglottic area. Because of these findings the case was considered suitable for radiation.

Involvement of the pre-epiglottic space and destruction of the thyroid cartilage by tumor can sometimes be demonstrated by cinefluorography, although they can be better demonstrated by enlarged lateral soft tissue films of the larynx.[1-5]

CASE 3. G.C., a 56 year old white male, hoarseness one year. Laryngoscopy showed a large fungating mass, easily bleeding, over the anterior two-thirds of the left true cord extending forward into the anterior commissure and down into the subglottic area. Anterior half of right cord involved.

Cinefluorography showed absence of ventricular recesses. There was good motion in the subglottic area (Fig. 3).

Course. Total laryngectomy, uneventful convalescence and discharge 12 days postoperative.

Comment. Cinefluorography revealed the extent of involvement of the ventricles in this case better than did laryngoscopy. One frame which was suggestive of a ventricle proved to be a transverse process of the cervical vertebrae, identified on motion in subsequent films. This would have been misleading in routine roentgenograms.

CASE 4. E.O'M., a 70 year old white female, admitted with progressive dysphagia for one year, with intermittent hoarseness.

Laryngoscopy showed a round, smooth, bleeding tumor about 3 cm below the arytenoids.

Biopsy—epidermoid carcinoma.

Further endoscopic examination showed a clear anterior wall, but did not demonstrate the lower edge of the tumor.

A Wookey type resection of the cervical esophagus was carried out, leaving the larynx in place. Reconstruction of the cervical esophageal segment was carried out six weeks after the original oper-

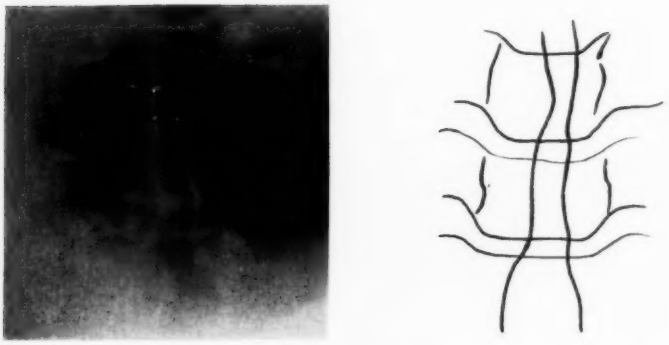

Fig. 7.—16 mm frame of esophageal speech showing open position of cervical esophagus on inspiration.

ation. Patient recovered well and is still alive, eight and one-half years after surgery.

Comment. At the time this patient was seen, cinefluorography was not available. It was extremely difficult, because of the large size of the tumor, to see even the lateral extent and to determine the degree

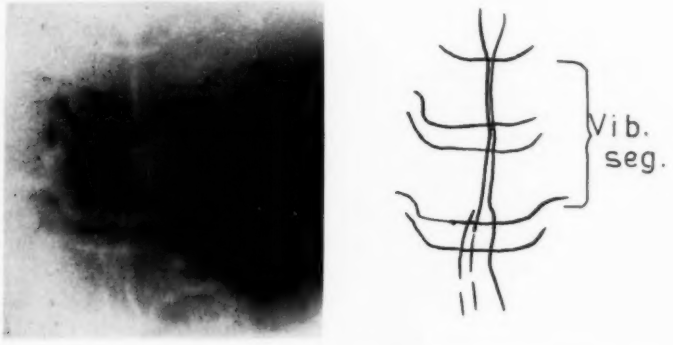

Fig. 8.—16 mm frame of esophageal speech showing the vibrating segment of cervical esophagus during phonation.

of fixation of surrounding tissues. Roentgenograms with barium swallow gave us a fairly good idea of the tumor's extent, but this was not definitely determined until the time of surgery.

The anterior wall of the laryngopharynx may be particularly difficult to evaluate by endoscopy, yet its freedom from neoplasm allows pharyngectomy without removal of the larynx in postcricoid cancer and this absence of involvement can often be demonstrated by cinefluorography.

Moderate dysphagia for solids, present since operation, was studied by cinefluorography, which showed a functioning cervical esophageal tube with good motion and no evidence of tumor.

Postoperative Applications. After laryngectomy, some patients develop dysphagia of different forms: 1) nasal regurgitation; 2) obstruction to the passage of food through the cervical esophagus; 3) regurgitation of partly digested food; 4) difficulty starting the bolus from the mouth into the pharynx. It is in the evaluation of these postoperative problems that cinefluorography has been particularly helpful.

CASE 5. A.G., a 53 year old white man referred for irradiation of residual tumor following laryngectomy.

6123 R delivered to pharynx.

Five years postoperatively patient developed CVA with hemiparesis.

Eight years postoperatively potient developed sudden dysphagia for solids, progressing in three weeks to dysphagia for liquids. Admitted to New Haven Hospital where the dysphagia gradually cleared over a period of one week.

Roentgenograms (Fig. 5) showed what could be considered a residual neoplasm. Cinefluorography, however, showed the rounded indentation on the posterior wall of the esophagus opening and flattening out so as to allow free passage of barium through the cervical esophageal lumen. This is strongly suggestive of a muscle bundle and not residual tumor (Fig. 4).

Comment. Cinefluorography showed the cervical mass contracting, changing shape and disappearing when a bolus passes the area. The mass represents the bunched up cricopharyngeus and inferior constrictor muscles which had been detached from their original cartilaginous attachments at laryngectomy.

In another patient (T.M.) with postlaryngectomy dysphagia, a larger mass appeared in the same area and that immediately above. After a 40 F. mercury dilator passed easily into the esophagus, motion picture studies showed a series of ineffective contractions of this mass. It is our impression that this represents both the inferior and middle constrictor, the latter having been separated from its attachment to the hyoid when this bone was removed during our routine technique.

CASE 6. J.D., a 64 year old white male, postlaryngectomy, uneventful convalescence. There was no fistula during his convalescence, but a tiny one appeared in a superior portion of the tracheal stoma, seven weeks postoperatively. This closed spontaneously within two weeks.

Nine months postoperatively a round "ulcer" was seen at the base of the tongue, at the site of the internal opening of the above-mentioned fistula. The patient reported the sensation of a foreign body in the throat and he brought up debris from this area into the mouth.

Cinefluorography showed a deep pocket or false diverticulum extending anteriorly at the base of the tongue at the upper limit of the surgical closure of the pharynx (Fig. 6). The recess could be seen to empty itself from time to time, although partially, and was freely mobile with the movements of the tongue and pharynx. The latter finding discredited any consideration of recurrent neoplasm.

Comment. The "exudate" found at the base of the tongue three months after laryngectomy was considered at first to be evidence of recurrent neoplasm. The cinefluorograms, however, revealed that this deep recess was partially filled with decomposed food and other debris from the mouth. This pocket has been found in other postlaryngectomy patients and represents an anterior outpouching the pharynx, probably the result of separation of the tissues along the line of closure where the pharynx joins the base of the tongue. It is probably an intermediate stage between a salivary fistula and primary healing.

By comparison, the case of J.Y., with postoperative fistula, was well documented by cinefluorography, which showed the origin, course, and internal size of the fistula while being distended by the barium mixture. Such information may be of value in persistent fistulas, where the question of surgical closure is being considered.

CASE 7. W.M., a 38 year old white male referred for laryngectomy because of radiation failure in a cord lesion. Laryngectomy convalescence was complicated by salivary fistula which healed spontaneously within two weeks.

The patient has since developed an excellent esophageal voice which has been studied by cinefluorography and sound track. An interesting finding in this case is that the vibrating segment of the cervical esophagus is rather long, probably two inches in length, and does not consist of a vibrating, sphincter-like ring of muscle as is sometimes described in the production of esophageal voice (Figs. 7 and 8).

Cinefluorography offers a satisfactory means of studying voice production in patients who have been operated by various modifications of laryngectomy or laryngopharyngectomy.

CONCLUSIONS

By adding the important element of motion to the roentgenographic study of the larynx and pharynx, cinefluorography offers the laryngologist an important technique in the pre-operative diagnosis of laryngeal cancer and in the postoperative evaluation of surgical complications.

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REFERENCES

1. Coutard, H., and Baclesse, F.: Roentgen Diagnosis during the Course of Roentgen Therapy of Epitheliomas of the Larynx and Hypopharynx. Amer. Jour. of Roentgenology 28:293 (Sept.) 1932.

2. Worning, B.: Roentgen Examination of Laryngeal and Hypopharyngeal Tumors. Acta Radiologica 15:8-23, 1934.

3. Pendergrass, E. P., and Young, B. R.: The Roentgen Diagnosis of Neoplasms of the Air and Food Passages, with Particular Reference to the Larynx. Radiology 36:197, 1941.

4. Fletcher, G. G., Old, J. W., and Loquvam, G. S.: A Topographic Approach to the Roentgenologic and Pathologic Examination of the Laryngopharyngeal Tumors. Radiology 63:361-380, 1954.

5. Baclesse, F.: Carcinoma of the Larynx. Brit. Jour. of Radiology, Suppl. 3, 1949.

6. Farinas, P. L.: Mucosography of the Respiratory Tract. Radiology 39:84-87, 1942.

7. Powers, W. E., McGee, H. H., Jr., and Seaman, W. B.: Contrast Examination of the Larynx and Pharynx. Radiology 68:169-178, 1957.

8. Gay, B. B., Jr.: A Roentgenologic Method for Evaluation of the Larynx and Pharynx. Amer. Jour. of Roentgenology 79:301, 1958.

9. Bachman, A. L.: The Radiologic Study of Some Normal and Abnormal Swallowing Mechanisms; Aspiration Phenomena and Cricopharyngeus Spasm. Laryngoscope 69:7:947-969 (July) 1959.

10. Tristan, T. A.: Methods of Cinefluorography. Med. Radiol. and Photog. 35: 38-44 (Nov. 2) 1959.

11. Ramsey, G. H., Watson, J. S., Gramiak, R., and Weinberg, S. A.: Cinefluorographic Analysis of the Mechanism of Swallowing Radiology 64:498-518 (Apr.) 1955.

LVIII

PHONATION

CLINICAL TESTING VERSUS ELECTROMYOGRAPHY

DAVID W. BREWER, M.D.

F. BERTRAM BRIESS

SYRACUSE, N. Y.

AND

K. FAABORG-ANDERSEN, M.D.

NYKOBING, DENMARK

By virtue of our training as laryngologists all of us have been primarily students of diseases of the larynx and their disturbing effect on its respiratory physiology. As a specialty group, we have devoted little time to the study of the physiology of phonation. This topic, however, has been the subject of considerable speculation by students of the voice (usually voice teachers but occasionally physicians). Much of what has been written necessarily has been based on empirical methods of voice training. This has caused the majority of us to categorize individual patients with voice problems as: a) surgical prospects because of visible lesions; b) candidates for long periods of voice rest; or c) psychosomatic problems. We have generally had little interest in the solution of voice problems seemingly unrelated to visible laryngeal pathology.

Attempting to bridge the gap between such voice terminology as divergence and falsetto and medical terminology such as thyro-arytenoid and hyperfunction is a time consuming and Herculean task.

The first clue came from Johannes Müller[1] who in 1837 indicated that the difference between natural voice and falsetto voice was pri-

From the Departments of Otolaryngology, S.U.N.Y. Upstate Medical Center at Syracuse, and Centralsygehuset, Nykobing, Falster, Denmark.

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marily due to a difference in function of the thyroarytenoid and the cricothyroid muscles. Gutzman[5] in 1905, using cadaver larynges, further explained Müller's work, demonstrating for students that the "fundamental" or natural voice was due primarily to thyroarytenoid muscle function with thickening of the vocal cord and vibration of the whole mass of the cord while falsetto was due to only "free-edge" vibration since the cord was greatly stretched by the action of the cricothyroid muscle.

Many reports of additional anatomical studies stressing various theories of the individual functions of the intrinsic laryngeal muscles have been published during the intervening years. Stroboscopic as well as normal and high speed motion picture studies of vocal cord movements have been misleading in certain instances since necessary protrusion of the tongue brings intrinsic muscles into play which further distort the intrinsic muscle activity. Yet, even newer methods of sound analysis have failed to show the specific amounts of individual muscle participation in the production of the many tones and effects of the full range of the human voice.

Even though normal laryngeal physiology has not been well understood, singers', screamers' or speakers' nodes have long been identified with voice strain or vocal abuse as their cause. It has been accepted by most that voice rest or reduction of vocal activity will produce at least temporary disappearance of these lesions. Permanent elimination and prophylaxis must come from a better understanding of the physiology and physio-pathology of the larynx.

In 1954, two new entirely independent investigations were begun which dealt specifically with the "gear-box of the voice," i.e., the intrinsic laryngeal muscles. Briess, in Syracuse, using clinical voice tests, measured the activity of these muscles, while Faaborg-Andersen, then in Copenhagen, Denmark, measured their activity electromyographically.

Based primarily on his previous thirty years of experience in the field of voice, Briess clinically determined the patient's ability to produce carefully chosen test sounds and phrases.[1] Successful completion of this clinical voice testing indicated a healthy voice and normal balance relationships of all of the five sets of intrinsic muscles. Failure during the tests indicated specific muscle imbalances. These imbal-

ances were identified and reported in terms of hyperfunction or hypofunction. Such imbalance was found to be associated with 25 specific symptoms such as lump feeling, dryness in the throat, tickle, cough, pain referred to the ear, tenderness over the arytenoid, etc. Persistence of these imbalances and symptoms was found to eventuate in abuse lesions such as edema, nodes, contact ulcers, polyps, etc. From a knowledge of symptoms and laryngoscopic findings alone, the laryngologist was able to predict the major muscle imbalance responsible for the patient's laryngeal difficulties. Based on the information gained from clinical voice testing, Briess designed for each patient a special therapeutic voice regimen[2] which, with laryngoscopic guidance, restored the muscles to normal balance. As a result of this, both lesions and symptoms disappeared without requiring surgical interference or voice rest. This was documented by over 1,000,000 feet of tape recordings and detailed interval laryngoscopic examinations during the treatment of over 300 patients.

Visible proof of altered and subsequently restored muscle balances, however, was lacking. It therefore was unacceptable to most laryngologists.

Faaborg-Andersen, completing his advanced specialty training in otolaryngology in Copenhagen, and hearing that electromyographic studies of the intrinsic laryngeal muscles were technically impossible, accepted the challenge and devised a technique for their study.[3] He was able to measure accurately the electrical activity in microvolts in each of two pre-selected single muscles and established for the first time the average range of activity for all intrinsic muscles with the exception of the lateral cricoarytenoid. His investigations demonstrated that "considerable increase in electrical activity occurred even before phonation was audible; that whispered voice and 'silent speech' evoked a similar but lesser degree of electrical activity than did ordinary phonation; that with increase in intensity or loudness there was no corresponding increase in electrical activity in the adductor muscles; nor was there increase in the action potential pattern with change of vowel. During increase in pitch within the same voice register electrical activity increased considerably, but with simultaneous shift in register only slight increase in electrical activity was evident.

"In patients with a paralyzed vocal cord in the electrical pattern changes during respiration, cough, swallow and variations in phona-

tion were qualitatively the same as in subjects with normally movable vocal cords.

"On the paretic side evidence of neurogenic paresis was found in all muscles except the cricothyroid in patients with an immovable vocal cord in the paramedian position.

"The results of his investigations did not support the Husson theory which assumes that at a given pitch the number of nerve impulses per second must equal the number of vibrations per second of the vocal cords. He found that the maximum discharge frequency in single motor units was only 30 per second, i.e., far below the vibrational frequency of the vocal cords."

In his published monograph of these investigations, his "findings were in agreement with the assumption that it is mainly the modified mucous membrane of the vocal cords which participates in the vibrations and that the vibrational frequency is determined by the active and passive tension exerted by the different intrinsic laryngeal muscles as a result of differences in degree of their contraction."

At the First International Voice Congress in Chicago in 1957, his initial report of this major contribution prompted us to discuss with him at once the possibility of simultaneously studying patients using both his and our techniques. Here at last might be a way of establishing by visual means the validity of our approach and of opening up a combined medium for study of additional unsolved laryngeal problems.

Thus, it was that we visited Faaborg-Andersen in his new department in the Central Hospital, Nykobing, Falster, Denmark, in April of 1959 to study clinically and electromyographically twelve of his patients, ten with laryngeal pathology presumably produced by vocal abuse, and two normal controls.

This initial investigation was designed to study similarities and differences in our methods of evaluation of intrinsic laryngeal muscle function and relationships with voice production. By combining our efforts and examining the same patients on the self same day, it was possible to obtain data useful for direct comparison. Three means of mensuration were used: 1) indications of major muscle imbalance

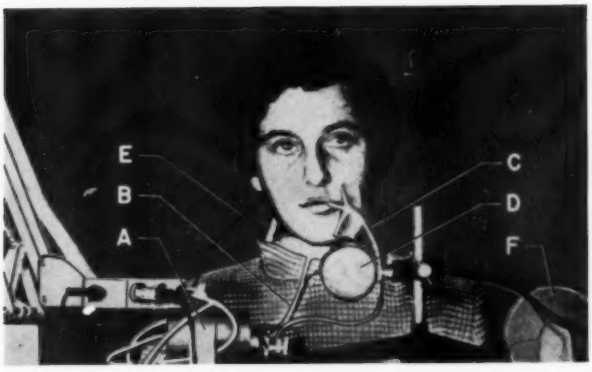


Fig. 1.—Experimental apparatus and arrangement. Left, the three channel electromyograph; right, the subject and the tape recorder with microphone (F). In front of the subject is seen the high-pass filter (A) inserted between the electromyograph and the electrodes. One needle electrode (B) is placed in the left cricothyroid muscle by insertion through the skin of the neck. Another needle electrode (C) is inserted through the mouth and placed in the vocal muscle. The third channel of the electromyograph is connected with a microphone (D) placed in front of the subject at a constant distance from the subject's mouth. A ground plate electrode (E) is attached to the back of the subject's neck.

by correlation of history and detailed description of even minor deviations from normal appearance of the larynx on indirect laryngoscopy (D.W.B.), the latter being performed independently by K.F.A. and D.W.B.; 2) clinical voice testing as expanded and reported by F.F.B.; 3) electromyographic study by the technique previously devised and reported by K.F.A. (Fig. 1).

METHOD OF PROCEDURE

A total of 12 patients comprised the group for examination. On each of seven patients the following procedure was carried out. For specific reasons indicated under the section entitled "Patients' Histories" it was impossible to perform the complete examination on five of the twelve. On two of these five EMG was performed but no sound tapes could be obtained.

1. History and otolaryngological examination.

2. Clinical voice testing recorded on tape.

3. Administration of intralaryngeal topical anesthesia.

4. Repeated clinical voice testing recorded on tape to detect any changes occasioned by use of the topical anesthesia (½ of 1% Tetracaine). This was discontinued by mutual agreement after no changes could be detected in three patients.

5. Insertion of electrodes into muscles in each case as indicated in Table I.

TABLE I

CASE NO.	ELECTRODES IN MUSCLES	EMG EILM OBTAINED	INTONATIONS TAPED DURING EMG	REMARKS
1	#1,2	No	No	
2	—	—	—	
3	1,2	Monitored only	No	
4	1,2;2,4;2,5	Yes	Yes	EMG microphone tracing poor
4	1,2;2,4;2,5	Yes	Yes	
5	—	—	—	
6	1,2	Yes	No	
7	4,5	Yes	Yes	
8	2,5	Yes	Yes	
9	1,2	Yes	Yes	
10	—	—	—	
11	2,4;3	Yes	Yes	
12	2	Yes	Yes	

6. Repeat clinical voice testing to ascertain any changes occasioned by placement of electrodes.

7. Simultaneous clinical voice testing and electromyographic tracings. In several instances, this was tape recorded after microphone interference problems were solved.

8. Repeat voice testing after removal of electrodes.

9. Comparison of results in the same patients as well as comparison of findings with all other studies.

For greater ease in identification of the intrinsic laryngeal muscles, and description of hypo- and hyperfunction, all three authors agreed to use the following, as routinely employed by D.W.B. and F.B.B.

Muscle No. 1—Thyroarytenoid.

Muscle No. 2—Cricothyroid.

Muscle No. 3—Lateral cricoarytenoid.

Muscle No. 4—Posterior cricoarytenoid.

Muscle No. 5—Interarytenoid.

Hyperfunction was identified as: 1+, 2+, 3+, 4+, 5+.

Hypofunction was identified as: 1—, 2—, 3—, 4—, 5—.

For example, No. 4: 4+ or No. 1: 2—.

In carrying out the investigation, all patients were those of K.F.A. Examinations were performed in the Research Laboratory of his Department of Otolaryngology at Centralsygehuset, Nykobing, Falster, Denmark. Voice history was taken by F.B.B. and D.W.B. Otolaryngological history was taken by K.F.A. Indirect laryngoscopy was performed by K.F.A. first and then D.W.B. The findings were not transmitted to F.B.B. until his voice testing was completed and he had given a prognosis as to the type of difficulty which the detected muscle imbalance should or would produce.

Muscles No. 1 and No. 2 were initially tested by requesting the patient to produce a phrase rich in "o" vowels consisting of eight to twelve syllables. By varying pitch from low to high and increasing and decreasing the musical intervals between the syllables an audible gap in sound production was provoked. The time-honored term for this gap is a "divergence." This gap represented a sudden collapse of muscle No. 1 and increased function of muscle No. 2. Normally, muscle No. 1 relaxes proportionately as muscle No. 2 contracts when pitch is raised. The frequency, in cycles per second, where the gap or divergency of muscle function was heard, indicated the voice type. There is a specific pitch for each of the ten major voice types. However, if muscles No. 4 and 4 showed imbalance, only a pseudo-divergence, unrelated to voice type, was heard. The relative propor-

Fig. 2.—Case No. 11 Retest

Band A: Phonation Scoop "O" Frequency 146-130-329 c.p.s.

Band B: Muscle No. 1. Clin. Voice Testing: With rise in pitch normally muscle No. 1 relaxes proportionately while muscle No. 2 contracts. Here, however, muscle No. 1 starts to relax, than suddenly contracts to plus 5 producing a divergence or gap in sound production.
EMG: Resting: 250 microvolts. Phonation: 200-550 microvolts.

Band C: Muscle No. 2. Clin. Voice Testing: Increasing to plus 3 and plus 4. EMG: Resting: 100 microvolts. Phonation: 500 microvolts.

tion of muscle No. 1 and No. 2 activity present in a particular voice determined whether it was of robust character with more participation of muscle No. 1 at a given pitch or of delicate character with more participation of muscle No. 2 at the same pitch.

Further testing of muscles No. 1 and No. 2 was done by designing specific phrases for each patient according to his voice type and character. These phrases were repeated from ten to fifty times. The degree of fatigue evidenced during this endurance test indicated the functioning condition of muscle No. 1. Hyper- or hypofunction of muscle No. 2 was determined by predominance or absence, as well as degree of inflexibility of free-edge vibration, called falsetto in male voices.

Muscles No. 3 and No. 4 were tested by noting the degree of breathiness evident on specific vowels and pitches in the same voice.

Activity of muscle No. 5 became evident either when staccato sounds produced fatigue or there was distortion of requested vowels.

By familiarity with such findings in thousands of voices previously tested, deviations from expected normal performance were indicated on a basis of hyperfunction of 1+ to 5+ and hypofunction of 1— to 5—.

The testing procedure could not be completed in cases with hypofunctioning voices—more than two pairs of muscles hypofunctioning —because of an accompanying subglottic undercompression. The amount of air pressure built up against the under surface of the vocal cords during the fraction of a second when the cords are closed during the phonation cycle is termed the subglottic compression. When this is too little the voice is weak.

The remainder of the routine was then carried out as indicated above. Following the completion of the initial examinations, the electromyograph recordings were studied by K.F.A. and the voice tests were restudied by F.B.B. Triplicate charts of the initial findings were prepared on completion of the patient's testing. Comparison of results, discussion, conclusion and summary were prepared some months after the patient investigation was completed. This gave still further objectivity to the results.

Following completion of the testing of patients, wide geographical separation of the authors necessitated preparation of duplicate sound tapes and duplicate EMG films for study. Following return of one of the early drafts of the findings K.F.A. reported that the range of mean amplitude of electrical activity measured in microvolts in adductor and abductor muscles, according to his previously established routine of measurement, did not correlate with the pre-EMG clinical voice testing as predicted by K.F.A. (These measurements are reported in each case history.) Of necessity, his findings were recorded in terms of "perhaps more than expected" or "perhaps less than expected" electrical activity since comparison was based on the range of activity encountered in his previous investigation.[3] He further explained this as follows: "In the intrinsic laryngeal muscles there is electrical activity of low amplitude and the single motor unit potentials cannot be distinguished from each other. In the adductor muscles the mean amplitude of the electrical activity is up to 200 microvolts in the absence of phonation during maximal relaxation and mostly 300-600 microvolts during phonation in high pitch. In

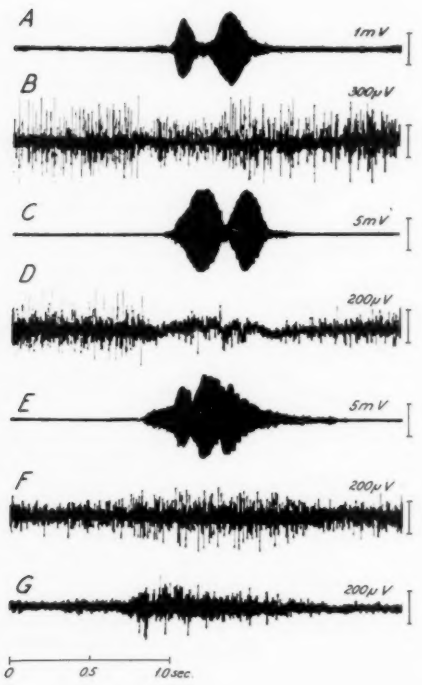


Fig. 3.—Case No. 4

Band A: Phonation: "Oh! Oh!" Frequency 207 and 196 c.p.s.

Band B: Muscle No. 4 *before* therapy. Clin. Voice Testing: Muscle No. 4 should relax as muscle No. 3 takes over to produce the staccato "Oh! Oh!" intonation. Before therapy the patient could not produce these sounds without breathiness due to extreme hyperfunction of the antagonistic muscle No. 3. No activity of muscle No. 4 was evident.

EMG: Resting: 390 microvolts. Phonation: 240 microvolts.

Band C: Phonation: "Oh! Oh!" Frequency 277 and 247 c.p.s.

Band D: Muscle No. 4 *after* therapy. Clin. Voice Testing: Here the same kind of staccato intonation again showed no activity of muscle No. 4. Absence of breathiness resulted from elimination of hyperfunction of muscle No. 3.

EMG: Resting: 400 microvolts. Phonation: 140 microvolts.

Band E: Phonation: Scoop "o" Frequency 220 to 440 c.p.s.

Band F: Muscle No. 4 *after* therapy. Clinical Voice Testing: The fact that the patient was able to produce a sustained tone without breathiness—even when pitch was raised—indicated that muscle No. 4 had returned to normal function.

EMG: Resting: 300 microvolts. Phonation: 400 microvolts.

Band G: Muscle No. 2 *after* therapy. Clinical Voice Testing: Increasing to 5+. This was possible before therapy and is normally expected with such a falsetto intonation.

EMG: Resting: 100 microvolts. Phonation: 350 microvolts.

the posterior cricoarytenoid muscle the mean amplitude of the electrical activity is 200-500 microvolts in the absence of phonation during maximal relaxation, and considerably reduces during phonation in high pitch." This finding was also reported previously by K.F.A.[3] "After all direct comparisons cannot be made between electromyograms obtained from different persons, or from the same person on different occasions, since even electromyograms taken from different places in the same muscle (although the point for picking up the impulses may be located only a few millimeters apart) can be completely different from each other, depending on where the electrodes are inserted into the muscle. During this investigation we have picked up impulses from several points in the single muscles. A mean amplitude of the electrical activity from several points up to 300 microvolts is called 'perhaps less than expected,' 300-600 microvolts normal activity, and more than 600 microvolts 'perhaps more than expected'." (Table III) (K.F.A.)

The electrical activity in the lateral cricoarytenoid muscle has not previously been described. "In this muscle there was found electrical activity up to 200 mv during quiet respiration in spite of every effort to achieve relaxation, just as in the other intrinsic laryngeal muscles. Even when the subjects held their breath this activity was observed. During phonation the electrical activity in the lateral cricoarytenoid muscle increased markedly. This increase began ca. 0.3 sec. before an audible tone was recorded by the microphone. At the end of phonation, when audible tone had ceased as indicated by the microphone recording, the increase in electrical activity had also disappeared (cf. Fig. 5)." (K.F.A.)

It was obvious after this report that the process of EMG either changed the existing muscle activity or that the muscle balance—proportional activity of antagonistic muscles—should have been studied for each single intonation produced during EMG testing. In retrospect this had been proposed as part of the original testing procedure as step No. 7, but was conceived as actually performing the clinical voice tests with the electrodes in place. This, however, was set aside by our deep interest in observing for the first time K.F.A.'s routine testing procedure of electromyography.

Review of sound tapes showed that intonations during clinical voice testing were quite different in pitch and muscle balance than

those produced during EMG. Therefore, single intonation clinical muscle activity assay was proposed by D.W.B. and F.B.B. and carried out. This required: 1) no reference to EMG films while performing this portion of the study; 2) review of tape recordings alone to determine points of onset and turn-off of the EMG motor; 3) duplication on sound tape of all sounds by each patient during EMG; 4) pitch identification of each single intonation; 5) accurate identification of No. 1, 2, 3, 4, and 5 muscle participation by aural analysis of each single intonation. With this information in booklet form the EMG duplicate films were viewed and correlation appeared feasible. Since this was a different view of EMG interpretation than that routinely used by K.F.A. and in order to fully discuss these new findings with him, a second meeting in Denmark was deemed essential.

After two days of conferences and demonstrations at the suggestion of D.W.B., a measurement of resting activity compared with single intonation phonation activity of each muscle studied yielded an approach agreeable to all three investigators.

The term "clinical muscle activity assay" was introduced to indicate on a plus or minus basis the function of an individual muscle *during a single intonation.*

Clinical muscle activity assay of a single intonation is impossible without the detailed familiarity with a patient's voice obtained from clinical voice testing.

Ratios of "resting" activity and phonation activity had not previously been measured electromyographically; instead the range of average activity for a series of intonations had been used as the criteria for function of a specific muscle.

Charting of predominating muscle imbalances indicated by patient's symptoms and physical findings on mirror laryngoscopy was also done. Familiarity with this technique had been gained from several hundred patients previously examined by D.W.B. and F.B.B. (in preparation for publication) (Table II).

At the suggestion of D.W.B. and F.B.B. time was allowed for testing of any patient of K.F.A.'s choice. Patient No. 11 was chosen

TABLE II

SYMPTOMS AND INDIRECT LARYNGOSCOPY - PREDOMINATING IMBALANCE

CASE NO.	SYMPTOM	INDIRECT LARYNGOSCOPY	INDICATED IMBALANCE
1	Weak voice Tires easily Left neck pain		More than 2 pairs Hypo Fatigue No. 1
		Tip rt. vocal process sl. pink Moderate thickening	Hyper No. 3 Hyper No. 3
	Throat clearing	Mucous strand junct. post ⅓	Imbalance No. 3 & No. 4 Hyper No. 3
2	Hoarseness	Pink cords & lt. false cord Lt. false cord overhangs true cord by 50%	Acute abuse Hyper No. 1 with fatigue to Hypo No. 1
3	Hoarseness	Mild bowing on phonation Moderate thickening No lesion	Hypo No. 2 & Hyper No. 5
4		Pink cords and false cords Posterior nodes at tips of vocal processes	Acute abuse Hyper No. 3 Hypo No. 4
5	Weak voice Tires easily	Slightly pink cords Mucous strand junction anterior ⅓ Under surface of cord Visible rt. more than lt.	Acute abuse Imbalance No. 3 & No. 4 Early node diathesis Hypo No. 1 or subglottic Undercompression Hypofunctioning voice
6	Rt. neck pain Tender rt. arytenoid	Short cords Moderate sup. surf. Edema Moderate thickening	Hyper No. 3 Hyper No. 3 Congenital
7		Mucous accumulation at tips of vocal processes Cords slightly thickened	Hypo No. 1 Hyper No. 3 Hypo No. 1 - Fatigue
8	Neck pain rt. & lt. Excessive mucus	Slight bowing on high tone Slightly pink cords Left arytenoid sits slightly anterior to rt. arytenoid	Hyper No. 1 Hypo No. 2 or Hyper No. 5 Acute abuse Hypo No. 4 or Post-traumatic
9	Hoarseness 2 yrs.	Transverse vibration Superior surface edema Lt. cord post. ⅓ mounded on phonation	Hyper No. 1 with Hypo No. 2 Hyper No. 1 Hypo No. 4 or Alternating Hyper No. 3 and No. 5
10	Neck pain rt. & lt. Rt. more intermittent Lump feeling		((Hyper No. 3 Hyper No. 1
11	None	Normal larynx	None
12	None	Normal larynx	None

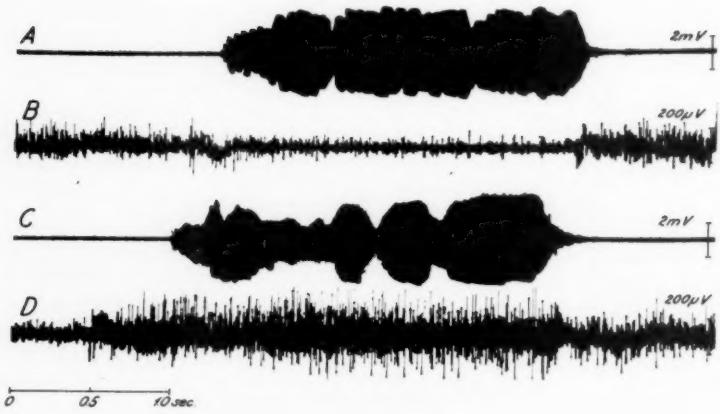


Fig. 4.—Case No. 12

Band A: Phonation "Oh" Frequency 87 c.p.s.

Band B: Muscle No. 2. Clin. Voice Testing: Very little activity is expected at such low pitch. It was estimated as minus 3.
EMG: Resting: 350 microvolts. Phonation: 80 microvolts.

Band C: Phonation "Oh" Frequency 349 c.p.s.

Band D: Muscle No. 2. Clin. Voice Testing: Essentially No. 1 participation and consequently No. 2 activity was estimated as plus 4.
EMG: Resting: 100 microvolts (120). Phonation: 500 microvolts.

since he was very co-operative and had been tested electromyographically on repeated occasions by K.F.A. in other investigations and demonstrations. This re-examination gave an additional opportunity to check F.B.B.'s clinical muscle activity assay. The sound tapes recorded during this EMG testing were immediately analyzed by F.B.B., and K.F.A. was able to observe this procedure and participate. Results were immediately written down. When the EMG films had been processed results were compared, and we were all utterly amazed at the close correlation between the clinical muscle activity assay reported by F.B.B. and the electrical activity reported by K.F.A. (cf. single tone comparisons Cases 4, 7, 9, 11, 12 and retesting Case 11) (Figs. 2, 3, 4 and 5).

RESULTS OF VOICE THERAPY

Although time was at a premium, it was possible for F.B.B. to treat two patients for approximately one hour each on four successive days. These patients are identified as Cases No. 2 and No. 4 in Table I. Unfortunately, it was impossible, because of excessive gagginess, to do EMG studies on Case No. 2. However, the patient's symptoms cleared and the overlying left false cord came back into normal position with definite tape recorded voice improvement during this short period. He returned at once to his night club singing. On repeated follow-up examinations, the patient's condition has regressed as predicted by F.B.B. since it was impossible to produce long-lasting results in such an extremely short therapy period. Yet, as might be expected, a summer vacation with decrease in vocal abuse has allowed the patient to remain partially improved.

Case No. 4 showed rapid regression followed by complete disappearance of bilateral nodes at the tips of the vocal processes in the short four-day period. This same patient had been treated previously over a period of months by two phoniatrists and had undergone two full weeks of total voice rest in the hospital, without noticeable improvement. However, phoniatrist No. 2 relieved the excessive hyperfunction of muscle No. 5 but had not reactivated muscle No. 4. As predicted by F.B.B., the nodes have reappeared since therapy while the patient has continued his regular vocal activities in the teaching profession. It is of special interest to note that the hypofunctioning muscle No. 4 was able to show normal function after therapy (Fig. 3).

COMPARISON OF RESULTS

The authors believe this to be the first investigation comparing symptoms and physical findings, clinical voice testing, and electromyographic testing simultaneously on patients.

By reference to Table III, it is demonstrated that there is accurate correlation between identification of predominating muscle imbalance determined by history and indirect laryngoscopy (D.W.B.) and clinical voice testing as routinely used by F.B.B.

Correlation between pre-EMG clinical voice testing and EMG mean amplitude of electrical activity for each muscle tested was im-

TABLE III
COMPARISON OF RESULTS

CASE NO.	HISTORY AND PHYS. FINDINGS	CLINICAL VOICE TESTING		INITIAL EMG INTERPRETATIONS	
1	#1 Hypo	#1 3—		#1 sl. but *not* l.t.e.*	
	#2 —	#2 2—		#2 Normal 200-300 m.sec.	
	#3 Hyper	#3 3+			
	#4 —	#4 3—			
	#5 —	#5 1+			
2	#1 Hypo	#1 3—		No EMG	
	#2 —	#2 2—			
	#3 —	#3 2—			
	#4 —	#4 2—			
	#5 —	#5 4+			
3	#1 —	#1 3—		#1 slight. p.l.t.e.**	
	#2 Hypo	#2 3—		#2 slight. p.l.t.e.**	
	#3 —	#3 2—			
	#4 —	#4 2—			
	#5 Hyper	#5 5+			
				Before Rx	After Rx
4	#1 —	Conversation	Teaching Voice		
		#1 3—	#1 3+	#1 p.m.t.e.	#1 normal
	#2 —	#2 Normal flexibility	#2 Normal flexibility	#2 normal	#2 normal
	#3 Hyper	#3 3+	#3 Normal flexibility	#3 —	#3 —
	#4 Hypo	#4 3—	#4 3+	#4 normal	#4
	#5 —	#5 3+	#5 3+	#5 normal	#5
5	#1 Hypo	Conversation	Loud Forced	No EMG	
		#1 2—	#1 4+		
	#2 —	#2 1—	#2 out		
	#3 (imbalance	#3 2+	#3 3—		
	#4 (imbalance	#4 2—	#4 3+		
	#5	#5 2—	#5 3+		
6	#1 —	Conversation	Yelling		
		#1 3—	#1 4+	#1 pronounced	
	#2 —	#2 2+	#2 out	#2 sl. p.l.t.e.	
	#3 —	#3 2+	#3 2—	#3 —	
	#4 —	#4 2—	#4 3+	#4 —	
	#5 —		#5	#5 —	
7	#1 Hypo	Conversation	Teaching Voice		
		#1 1—	#1 3+	#1 —	
	#2 —	#2 Normal flexibility	#2 3—	#2 —	
	#3 Hyper	#3 3+	#3 3—	#3 —	
	#4 —	#4 2—	#4 4+	#4 Normal	
	#5 —	#5 Normal flexibility	#5 4+	#5 —	
8	#1 Hyper	#1 4+		#1 —	
	#2 Hypo	#2 4—		#2 Normal	
	#3 —	#3 2—		#3 sl. p.l.t.e.	
	#4 —	#4 1+		#4 —	
	#5 Hyper	#5 1+		#5 —	
9	#1 Hyper	#1 4+		#1 sl. p.l.t.e.	
	#2 Hypo	#2 4— to out		#2 Normal	
	#3 —	#3 —		#3 —	
	#4 —	#4 —		#4 —	
	#5 —	#5 —		#5 —	
10	#1 Hyper	Conversation	Dr.'s Exam. Tongue Out		
		#1 1+	#1 1+	No EMG	
	#2 —	#2 1—	#2 1+		
	#3 Hyper	#3 1+	#3 1+		
	#4 Hypo	#4 1—	#4 1—		
	#5 —	#5 ?	#5 1—		
11	#1 —	#1 (		#1 —	
	#2 —	#2 (		#2 Normal	
	#3 —	#3 (Healthy Voice		#3 Normal	
	#4 —	#4 (		#4 Normal	
	#5 —	#5 (		#5 —	
12	#1 —	#1 (		#1 —	
	#2 —	#2 (		#2 Normal	
	#3 —	#3 (Healthy Voice		#3 —	
	#4 —	#4 (		#4 —	
	#5 —	#5 (		#5 —	

* Less than expected
** Perhaps less than expected

possible (Table III). Review of all sound tapes showed that patients routinely produced entirely different sounds with respect to pitch, volume and muscle balance during these two procedures.

Full positive statistical correlation was found between clinical assay of muscle activity by F.B.B. and recorded electrical activity of these same muscles by EMG as determined by K.F.A. when compared in each separate intonation.

The effects of voice therapy have been shown to produce a specific, predicted change in intrinsic laryngeal muscle electrical activity with concomitant relief of symptoms and disappearance of lesions.

COMMENT

Completion of the full examination schedule was not possible in all cases because of such technical difficulties as patient's unsuitability for EMG testing (too gaggy, too apprehensive); unshielded cable from tape recorder to microphone which interfered with the EMG machine and had to be replaced; and difficulties in one case in identification of intonations on EMG microphone tracing.

It was particularly valuable to deal with patients unable to speak English and to find that their voices responded as accurately to the routine clinical testing. It was necessary to prepare patients for EMG in that they were asked to attempt certain sounds that they routinely had not been accustomed to produce. For example, many persons do not use falsetto in their daily conversation, but for testing such an attempt was necessary. Several patients, unable to do this on their own, were capable of producing a falsetto with the electrodes in place. This may have been due to increased familiarity with the desires of F.B.B. during EMG testing.

Case No. 4 showed a distinct change after four therapy sessions. First, the lesions originally visualized had disappeared and, secondly, the hypofunction of muscle No. 4 had been temporarily eliminated so that both clinically and electromyographically it showed its improvement to normal function. Thirdly, symptoms disappeared (Fig. 3).

Such function of muscle No. 4, known as normal to F.B.B. was distinctly abnormal to K.F.A. The composite American voice is able

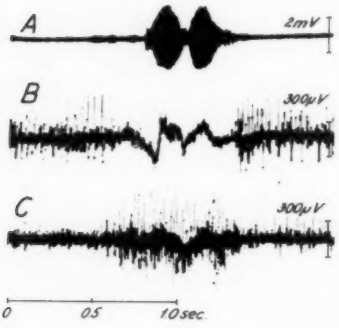


Fig. 5.—Case No. 11

Band A: Phonation: "Oh! Oh!" 247 and 196 c.p.c. This intonation designed to investigate balance of muscles No. 3 and 4 which are responsible for posterior closure.

Band B: Muscle No. 4. Clinical Voice Testing: No activity. Here muscle No. 5 has taken over, replacing muscle No. 4 to produce an attempted balance with muscle No. 3.

EMG: Resting: 600 microvolts. Phonation: 100 microvolts.

Band C: Muscle No. 3. Clin. Voice Testing: For each "Oh!" there was increase to plus 4 followed by sudden drop to no activity when the tone was the loudest, then again an increase to plus 4.

EMG: Resting: 200 microvolts. Phonation: 800 microvolts.

to show flexible interplay of muscles No. 3 and No. 4, whereas, except in the trained Danish voice, muscle No. 5 substitutes for No. 4, leaving No. 4 hypofunctioning.

Several voices, Cases No. 1, 2, and 3, were classified as hypofunctioning voices. This is a well known condition in clinical voice testing and is present when more than two pairs of the five pairs of intrinsic muscles are excessively hypofunctioning. The audible evidence of this is a voice of little volume. There is always subglottic undercompression present in such patients.

As previously reported,[1] in a healthy voice mechanism No. 1 muscle relaxes proportionately when No. 2 contracts and vice versa. In Danish voices, a predominating No. 1 (thyroarytenoid) function exists. In the presence of subglottic overcompression when pitch is

raised in such voices, No. 1 cannot relax but will hyperfunction (Fig. 2). Case No. 11 (retest) displayed a simultaneous increase in function of No. 1 and No. 2 muscles which, because of subglottic overcompression, showed an acute divergence. This is the first visual proof of the existence of this long recognized but easily misinterpreted audible phenomenon (cf. Fig. 2).

Since there are no two voices identical in every respect, the ratios of activity of No. 1 and No. 2 with No. 3, No. 4 and No. 5 differ with voice type and voice character. Clinical voice testing determines the existing ratios only by comparison with expected ratios. This is necessarily based on attempted performance during four essential tests. The expected ratios must be judged from experience. This is gained from testing and working with thousands of voices in this manner. Ratios change in a single voice when pitch is changed. However, at the same identical pitch different ratios are expected in voices differing in voice type and degree of voice character. Any deviation from the expected ratio in a particular voice is identified as plus or minus.

Having once become familiar with a voice clinical muscle activity assay involving a single tone irrespective of pitch can be made similarly by plus or minus deviation from the expected ratio of activity (Fig. 4).

From the personal interview, the voice diagnostician becomes familiar with the patient's daily voice habits and symptoms. During clinical voice testing, identification of kinds of abuse and the muscle imbalances associated with each kind of abuse is also accomplished.

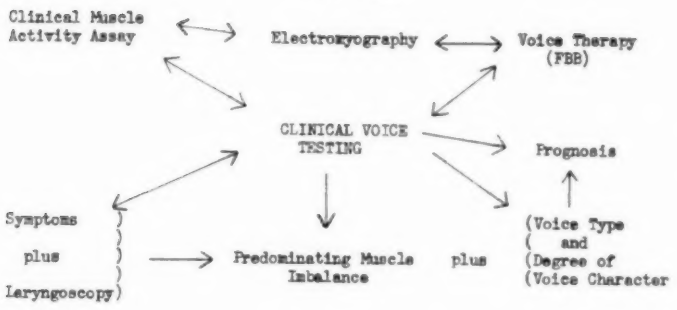
Selecting the predominating abuse and having already determined its associated muscle imbalance and projecting the consequences in the light of knowing both voice type and degree of voice character makes possible prognosis of lesion present or incipient.

Laryngoscopy identifies presence and extent of lesions and often type of lesion. Corroborative laboratory studies must not be neglected. Although F.B.B. was not given any information regarding laryngeal findings in all 12 patients comparison of his prognosis and findings of indirect laryngoscopy showed positive statistical correlation (Table IV).

TABLE IV

CASE NO.	CLINICAL VOICE TESTING		VOICE TYPE	VOICE CHARACTER	PROGNOSIS
1	#1 3— #2 2— #3 3+ #4 3— #5 1+		High	Delicate	Contact Ulcer
2	#1 3— #2 2— #3 2— #4 2— #5 4+		Medium	Robust	Thickening after Edema
3	#1 3— #2 3— #3 2— #4 2— #5 5+		—	—	Dysphonia Plica
4	Conversation #1 3— #2 Normal flexibility #3 3+ #4 3— #5 3+	Teaching Voice #1 3+ #2 Normal flexibility #3 Normal flexibility #4 3+ #5 3+	High	Delicate	Contact Ulcer + Nodes Redness - Air Waste
5	Conversation #1 2— #2 1— #3 2+ #4 2— #5 2—	Loud Forced #1 4+ #2 out #3 3— #4 3+ #5 3+	Low	—	Voice trouble whole life
6	Conversation #1 3— #2 2+ #3 2+ #4 2—	Yelling #1 4+ #2 out #3 2— #4 3+ #5	—	—	Conversation - Node - Edema Yelling - Polyp - Thickening
7	Conversation #1 1— #2 Normal flexibility #3 3+ #4 2— #5 Normal flexibility	Teaching Voice #1 3+ #2 3— #3 3— #4 4+ #5 4+	High	Delicate	Contact Ulcer if #1 Voice Therapy continues
8	#1 4+ #2 4— #3 2— #4 1+ #5 1+		Medium High	Robust —	No prognosis Voice trouble whole life
9	#1 4+ #2 4— to out #3 — #4 — #5 —				
10	Conversation #1 1+ #2 1— #3 1+ #4 1— #5 ?	Dr.'s Exam. Tongue Out #1 1+ #2 1+ #3 1+ #4 1— #5 1—	Medium	Robust	No prognosis
11	Healthy Voice		High	Robust	No prognosis
12	Healthy Voice		High	Robust	No prognosis

Chart 1



D.W.B. and F.B.B. have routinely, in their study of patients with voice problems prior to this investigation, correlated symptoms, laryngeal findings, and predominating muscle imbalance as determined by clinical voice testing. In this present investigation it was possible for them to predict accurately the predominating muscle imbalance to be found on clinical voice testing from knowing only symptoms and laryngeal findings. This was done without reference to any other information eight months after the initial examination without voice tape recordings or electromyographic findings available.

This procedure has a two-fold value. It enables the laryngologist, familiar with the head and neck symptoms and laryngeal findings of vocal abuse, to suspect the predominating muscle imbalance to be found later by the competent voice diagnostician and voice therapist. In addition, it indicates the patient's tissue reaction to the predominating abuse. This aids the laryngologist in prognosis and his evaluation of the necessary measures to be taken for relief of symptoms and lesion of each particular patient.

The relationships of the above major findings of this investigation may be indicated in chart form (Chart 1).

SUMMARY AND CONCLUSIONS

Activities of the intrinsic laryngeal muscles have been studied on the same patients on the same day by three separate techniques:

1) identification of major muscle imbalance by correlation of history and laryngoscopic findings; 2) clinical voice testing; and 3) electromyography. Directly comparable results have been obtained. These results indicate that:

1. Healthy phonation basically is dependent on flexible balances of the inter-related sets of intrinsic laryngeal muscles.

2. Unhealthy phonation or vocal abuse was regularly identified with imbalance of these same intrinsic muscles.

3. It is now possible, as an office procedure, for laryngologists, familiar with the head and neck symptoms as well as the laryngoscopic findings of vocal abuse, to suspect the responsible predominating muscle imbalance of the intrinsic laryngeal muscles.

4. Ratios of normal balances as well as imbalances in voice production were identifiable by clinical voice testing of F.B.B.

5. Based on clinical voice testing, it has been demonstrated that the amount of activity of these muscles required to produce voice sounds can be measured clinically both qualitatively and quantitatively even in a single intonation. This new technique has been termed clinical muscle activity assay.

6. In single intonations the electromyographically demonstrated ratio between "resting" and phonation amplitudes measured in microvalts is directly comparable with clinical muscle activity assay. Of 75 intonations so studied, full positive statistical correlation was found.

7. Clinical muscle activity assay can now be used as an additional clinical research tool to measure accurately the amount of vocal abuse occurring in each instance of imbalanced muscle activity in any individual voice.

8. F.B.B. and K.F.A. jointly present for the first time visual demonstration of divergence of function of thyroarytenoid and cricothyroid muscles.

9. K.F.A. for the first time presents in this paper a demonstration of the activity of muscle No. 3 or the lateral cricoarytenoid muscle.

Although he had examined this muscle in previous instances the report of its activity has not been previously published.

10. It has been found that by study of single intonations, electromyography is even more accurate than previously realized. As a valuable laboratory instrument in laryngeal research, it must now be placed foremost in our armamentarium.

11. The results of therapy in Case No. 4 are particularly significant. There was electromyographic confirmation of the results of the unique regimen of voice therapy of F.B.B. By this means, existing intrinsic laryngeal muscle imbalance was relieved with a concurrent disappearance of symptoms and a return of normal laryngeal appearance.

On the basis of these findings, it appears evident that a new school of voice diagnosis and therapy must be initiated. Here, well qualified individuals may be thoroughly trained in the techniques outlined above With scientific training of this caliber, the great need for competent voice therapists can be met. By association with such therapists, the laryngologist who becomes familiar with clinical evidence of intrinsic laryngeal muscle imbalance can be fully effective in his management of patients with the many head and neck symptoms related to vocal abuse. We hope that this report will provide the stimulus for many additional research investigations in our chosen field of laryngology.

Last spring, we chose as the title of this paper "Phonation: Clinical Testing versus Electromyography." As a result of this investigation, we think it should now read "Phonation: Clinical Voice Testing and Electromyography."

1100 E. Genesee St.

(Detailed data, too voluminous for inclusion here, may be obtained from the authors.)

REFERENCES

1. Briess, F. Bertram: Voice Therapy, Part I. Identification of Specific Laryngeal Muscle Dysfunction by Voice Testing. A.M.A. Arch. of Otolaryng. 66:375-382 (Oct.) 1957.

2. Briess, F. Bertram: Voice Therapy, Part II. Essential Treatment Phases of Specific Laryngeal Muscle Dysfunction. A.M.A. Arch. of Otolaryng. 69:61-69 (Jan.) 1959.

3. Faaborg-Andersen, K.: Electromyographic Investigation of Intrinsic Laryngeal Muscles in Humans. Acta Physiologica Scandinavica, Vol. 41, Supplementum 140, Feb. 8, 1957.

4. Müller, Johannes: Handbuch der Physiologie des Menschen. Band 2, 1ste Teil, Koblenz 1837, pp. 133-245.

5. Gutzmann, H.: Physiologie der Stimme und Sprache. 1909, p. 10, Friedrich Vieweg und Sohn, Braunschweig.

LIX

POSTERIOR CHOANAL ATRESIA

DANIEL C. BAKER, JR., M.D.

JULES G. WALTNER, M.D.
(by invitation)

AND

WILLIAM NOVICK, M.D.
(by invitation)

NEW YORK, N. Y.

Atresia of the posterior nares is probably a common congenital anomaly. In recent years, there has been a marked increase in the number of papers dealing with this subject. This is due to two factors, one, the relation of bilateral choanal atresia to respiratory and feeding difficulties in the newborn, and the other, the increased interest in the surgical correction of the condition.

It is important for the otolaryngologist to think of choanal atresia whenever respiratory obstruction is present in the newborn. In addition, the possibility of this defect being the cause of unilateral nasal obstruction in children as well as adults has to be considered.

This presentation will show our experience with 15 cases of atresia of the posterior nares.

The excellent contribution of others to the subject has been most helpful. Boyd[1] made a very thorough study of congenital atresia of the posterior nares. Hanckel[2] reviewed the literature and noted that Otto described the anomaly in 1831. Hanckel discussed the theories as to the development of the disorder. It may be the result of a persistence of the nasobuccal membrane; or a medial overgrowth of the vertical and horizontal palatal processes; or a persistence of the

From the Department of Otolaryngology, Presbyterian Hospital and the College of Physicians and Surgeons, Columbia University, New York, New York.

nasopharyngeal membrane. Hanckel reported a case in an infant who had severe respiratory difficulties at birth. A tracheotomy was necessary. This was followed later by a transpalatal approach for removal of the bony atresia.

Beinfield[3-7] has described the symptoms of the newborn with bilateral choanal atresia. He has stressed its relation to asphyxia and the emergency nature of the problem. He has described the methods of correcting the condition by an intranasal approach.

Morrow[8] reported three cases of bilateral atresia of the posterior nares in the newborn. All were operated on successfully.

Hough[9] has described the mechanisms of asphyxia in bilateral choanal atresia. A newborn infant will not automatically open its mouth to breathe, if it cannot breathe through its nose. This is the important factor in the respiratory difficulties.

Wilson[10] and Rawdon and Baade[11] have described the surgical treatment of the condition by the transpalatal approach.

All of the authors mentioned have covered the subject of posterior choanal atresia very adequately. No attempt will be made to discuss the phases of the subject that are already well known. The experience gained by our study of 15 patients with this congenital disorder might be of value to others. It is presented with this object in mind.

ANALYSIS OF CASES

None of the cases presented were classified in the emergency group as mentioned by Beinfield and Morrow. There was no instance in our hospital where a diagnosis of bilateral atresia of the posterior nares was made at birth or shortly thereafter. All newborn infants with emergency respiratory disturbances are usually seen by a member of the otolaryngological service. In addition, infants with respiratory difficulties are referred to Babies Hospital from other institutions. There are a large number of patients. It is difficult to give a reason why we have not had infants requiring emergency nasal surgery at birth. It is possible that the patients are adequately treated elsewhere, and that there is no reason for referral. It is also possible that such

infants die from asphyxia due to lack of proper diagnosis and recognition of choanal atresia.

In our group there were 3 children with bilateral bony atresia of the posterior nares. All were operated on by a transpalatal approach. The youngest was 22 months. Two children of the group had bilateral membranous atresia and were operated on by the intranasal route. All 5 of these children were less than 5 years of age at the time of surgery. How they were able to survive the bilateral atresia of the posterior nares at birth is best explained by the fact that they developed the ability to breathe through their mouth shortly after birth. All of these infants had respiratory difficulty and disturbances in feeding at birth. They were not seen by our service until after they had adjusted to their disability.

After surgery was performed on these children, it was necessary to leave a catheter in place until healing had occurred and a lumen had been established. It was important to carry out dilatations after the catheters were removed. Treatment sometimes required six months or longer.

There were ten patients with unilateral posterior choanal atresia. The youngest case recognized in this group was one month of age. The oldest was 57 years of age. The unilateral cases had no respiratory or feeding problems. A persistent anterior nasal discharge from the obstructed side of the nose was the only constant symptom. Two patients had an infection of the sinuses on the involved side. It should be mentioned that Beinfield considers unilateral atresia of the posterior nares in the infant as potentially dangerous. If the infant's open nasal chamber becomes obstructed, as a result of infection or even position in a crib, asphyxia may result.

All of the patients had either an intranasal or transpalatal operation for the atresia. In a group of eight adults, seven had a previous submucous resection. The submucous resection was not successful in 5 cases, and a transpalatal operation was performed.

Care has to be taken during the operation so that mucosal flaps are preserved both from the nasal side as well as the pharyngeal side of the atresia. The flaps are used to cover the denuded bone. This was easier to accomplish when the transpalatal approach was used.

Some authors have recommended the use of a skin graft after the atresia was removed. This was not necessary in any of these patients.

Not all of the patients were successfully taken care of. There was no good follow-up in five of the patients. It can be presumed that they sought help elsewhere.

The patients on whom the transpalatal approach was performed had the best result. From a surgical standpoint, it is the logical approach to the area involved. There were no surgical complications. Healing of the palatal incision was by first intention. There was not as much discomfort as would be present from a tonsillectomy.

After the atresia was removed, a polyethylene tube was inserted. The tube extended from the anterior nares to the nasopharynx. The tube was removed once or twice a week and the nose was washed out. The tube was then reinserted. This adds to the comfort of the patient, as well as keeping down secondary infection.

The tube was completely removed on an average of 6 weeks after surgery. It became apparent to us that the operated area would then become smaller from above downward, leaving a small round opening along the floor of the posterior nares. The narrowing was due to fibrous tissue formation. In order to get a satisfactory opening, it was necessary to reopen the fibrous tissue with a knife and to carry out dilatations. The latter was not too successful. In order to solve this probelm, after the fibrous tissue was incised, a piece of cleared x-ray film was inserted through the stenosed area. The plastic film was cut so that it could be introduced into the nasal chamber. It was of such length that it extended from the nasal tip to the nasopharynx. The nasal tip kept the strip in proper position. The posterior edge of the plastic material was readily visible by posterior rhinoscopy. No reaction was seen even when left in the nose for three months. The use of the cleared plastic x-ray film was most helpful in obtaining a final good result.

SUMMARY

Fifteen patients were observed with atresia of the posterior choanae. There were ten unilateral and five bilateral cases. Ten of the patients had a bony atresia and five were of the membranous type.

Adequate surgery can be performed by either the intranasal or transpalatal route. The latter was found to be more satisfactory in our experience.

The use of cleared x-ray film, introduced in a vertical plane through the posterior choana, allows for better epithelialization and helps to prevent stenosis of the upper part of the posterior nares. The lumen thus obtained is more nearly normal, than if a polyethylene tube is used alone.

903 Park Ave.

REFERENCES

1. Boyd, H. M. E.: Congenital Atresia of the Posterior Nares. Arch. Otolaryng. 41:261, 1945.

2. Hanckel, R. W.: Bilateral Choanal Atresia. Annals of Otology, Rhinology and Laryngology 58:852, 1949.

3. Beinfield, H.: Treatment of Complete Unilateral Bony Atresia of the Posterior Nares. Arch. Otolaryng. 53:530, 1951.

4. Beinfield, H.: Bilateral Bony Atresia of the Posterior Nares in a One-month Premature Infant Who Survived. J. Pediat. 45:679, 1954.

5. Beinfield, H.: Surgical Management of Complete and Incomplete Bony Atresia of the Posterior Nares. Trans. Am. Acad. Ophth. and Otolaryng. 60:778, 1958.

6. Beinfield, H.: A Forgotten Cause of Infant Suffocation. The Possible Relation Between Atresia of the Posterior Nares to Asphyxia Neonatorum and Sudden Infant Death. J. Int. Col. Surg. 22:447, 1954.

7. Beinfield, H.: Surgery for Bilateral Bony Atresia of the Posterior Nares in the Newborn. Arch. Otolaryng. 70:1, 1959.

8. Morrow, R.: Bilateral Congenital Choanal Atresia: A Report of Three Cases Corrected Surgically in the Newborn. Annals of Otology, Rhinology and Laryngology 66:135, 1957.

9. Hough, J. V. D.: The Mechanism of Asphyxia in Bilateral Choanal Atresia. The Technique of Its Surgical Correction in the Newborn. Southern Med. J. 48: 588, 1955.

10. Wilson, C. P.: Treatment of Choanal Atresia. J. Laryng. and Otol. 71:616, 1957.

11. Rawdon, R. E., and Baade, E. A.: The Transpalatal Approach to Choanal Atresia. Trans. American Otorhin. Soc. Plas. Surg. 3:27, 1960.

LX

FINDINGS REFERABLE TO THE UPPER PART OF THE RESPIRATORY TRACT IN WEGENER'S GRANULOMATOSIS

HENRY A. BROWN, M.D.
LEWIS B. WOOLNER, M.D.
ROCHESTER, MINN.

In this paper we shall present reports upon six patients who had the presenting symptoms of infection of the upper part of the respiratory tract who later gave evidence of a generalized disease process in which the symptoms and signs of glomerulonephritis were prominent. Necropsy was done in four cases, and in these the pathologic diagnosis was periarteritis nodosa. In one patient who died with the diagnosis of acute nephritis, the diagnosis of periarteritis nodosa was assumed from the course of the disease and the multiple systemic involvement. In the patient who was still living two years after the onset, at the time of this report, the diagnosis of periarteritis nodosa was made on the same basis.

Of special interest is the speculation as to whether the periarteritis nodosa developed secondary to the infection in the upper part of the respiratory tract or whether the condition merely represents a local manifestation of periarteritis nodosa appearing initially in the tissues of the upper part of the respiratory tract.

REVIEW OF THE LITERATURE

In 1936 and 1939 Wegener[1,2] presented three cases in which destructive granulomatous rhinitis was associated with prominent pulmonary symptoms, glomerulonephritis and generalized angiitis. He realized that this unusual clinicopathologic symptom complex did

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

not apply to any known specific granulomatous disease, and he recognized that except for the granulomatous lesions found in the respiratory tract, the disease was very similar to periarteritis nodosa. Wegener[1,2] and others[3,4] have considered the disease a variant of periarteritis nodosa.

There is some debate as to whether Wegener's granulomatosis and the so-called lethal midline granuloma are somewhat similar but actually different disease processes or merely synonyms for the same disorder.[5-8] In describing his cases Wegener obviously was describing instances of midline granulomas, and he was the first to demonstrate the presence of generalized periarteritis nodosa in this condition at necropsy. On the basis of later reports in the literature it seems doubtful that any real distinction between the two conditions can be made, although Atkins and Eisman[9,10] have suggested that the difference lies in the location of the lesions. If the nose, sinuses and pharynx are involved, the lesion is lethal granuloma; but if the larynx, trachea and lungs are involved, the process should be termed "Wegener's granulomatosis." There seems to be little merit in such an artificial division, however, in view of the fact that Wegener was reporting on midline granulomas, and since granulomatous lesions often are found in the nasal chambers, sinuses, pharynx, larynx, trachea and lungs of the same patient. The modern tendency seems to be to include as many lesions as possible under a single heading rather than to produce artificial divisions in essentially similar conditions. The underlying periarteritis nodosa seems to be the important pathologic condition in these lesions, and therefore "Wegener's granulomatosis" and "midline granuloma" should be considered synonyms.

The exact causation of Wegener's granulomatosis is unknown, but most recent authors agree that it is a disease of hypersensitivity. Wilson and Alexander[11] wrote that in man the lesions of periarteritis nodosa have been found at necropsy in the bodies of persons who in life had had the presenting symptoms of various forms of allergy.[12] Granulomas, the other finding in Wegener's granulomatosis, have been produced experimentally by injection of egg white into the subcutaneous tissue of a sensitized animal.[13]

Blatt and associates[7] suggested that some noxious substance, such as a chemical, physical agent or more likely an infectious organism, might bring about local tissue destruction in the respiratory tract

which, acting as an auto-antigen, might react with auto-antibodies and produce a state of hypersensitivity. Stratton and associates[8] wrote that bacterial or chemical agents associated with infections of the upper part of the respiratory tract may produce a localized hypersensitivity reaction in the respiratory tract, sensitize the body generally and produce the arterial lesions associated with periarteritis nodosa. Some authors have felt that the sulfonamide compounds or antibiotic agents[12,14] used in the treatment of infections of the upper part of the respiratory tract may have been responsible for the development of granulomatous lesions of the respiratory tract and subsequent generalized periarteritis nodosa; however, instances of Wegener's granulomatosis have developed when sulfonamides or antibiotic agents have not been administered.[1,8]

Godman and Churg[6] said that Wegener's granulomatosis has clinically recognizable manifestations, a particular natural history and anatomically diagnostic features which distinguish the disease from the ordinary form of periarteritis nodosa, but they allowed that the two are close relatives. They wrote that the vascular lesions associated with Wegener's granulomatosis closely resemble those of the microscopic form of periarteritis nodosa.

Godman and Churg[6] have listed the pathologic characteristics of Wegener's granulomatosis as follows:

1. A necrotizing granulomatous process involving the upper or lower part of the respiratory tract, or both.

2. Generalized focal necrosing vasculitis involving both arteries and veins, almost always in the lungs and more or less widely disseminated in other sites.

3. Glomerulitis characterized by necrosis of loops or lobes of the capillary tuft, adhesions and development as a granulomatous lesion.

CLINICAL PICTURE OF WEGENER'S GRANULOMATOSIS

The following description of the manifestations of Wegener's granulomatosis was evolved by review of cases reported in the literature,[8,10,14-26] especially the excellent summation of clinical observations by Fahey and associates.[21] The disease affects men and women of all ages, most frequently in the fourth and fifth decades.

The patient initially complains of an acute infection of the upper part of the respiratory tract; or occasionally a cough or thoracic discomfort may be the first symptom. Bloody nasal discharge, symptoms of acute sinusitis or hoarseness or the symptoms and signs of infection of the ear may develop. The process continues to advance in spite of vigorous treatment, including use of the sulfonamide compounds and antibodies. Staphylococcus aureus and less frequently a hemolytic streptococcus, a pneumococcus, species of Proteus or other organisms may be cultured from swabbings of the nose or throat, but the patient does not improve after the organisms have been eradicated. Edema over the maxilla, ocular proptosis, antro-alveolar fistula or even saddleback nasal deformity may develop, but, conversely, there may be no external manifestations of the disease, in spite of varying degrees of intranasal disease.

An infection of the ear may persist in a subacute degree, producing some loss of hearing or possibly a collection of fluid behind the tympanic membrane. Occasionally, however, the infection of the ear may become the most active part of the disease process, producing severe neurosensory deafness or facial paralysis, and may require surgical treatment for mastoid disease. Intranasal examination carried out early in the disease may seem to indicate that ordinary acute rhinosinusitis is at hand. A little later the nasal septum or turbinates may take on a granular appearance and bleed somewhat easily when touched or when adherent scales are removed. Still later definite granulomas may appear in the nose, most frequently on the nasal septum. Late in the disease both nasal chambers may be filled with bloody crusts, and there may be extensive destruction of the intranasal structures, including the septum, or the nasal chambers may be filled with granulomatous tissue.

Ulcers may appear about the pharynx, mouth or tongue, and results of biopsy, culturing and inoculation of guinea pigs with swabbings will fail to establish the cause of the disease. Early in the disease acute laryngitis may appear to be present, and later granulomatous ulcers, covered by adherent crusts, may arise in the larynx. Occasionally the larynx may be extensively involved, with or without significant symptoms referable to the nose or ears, and subglottic granulomatous masses may produce sufficient respiratory obstruction to necessitate tracheotomy.

Patients who have Wegener's granulomatosis usually present constitutional symptoms out of proportion to the clinical findings. The patients are almost always febrile, lose weight, become anemic, and have leukocytosis and an elevated sedimentation rate.

The duration of the disease is short. Six months is the average length of time from the initial symptoms until death, although the patient occasionally may live for two or more years.

At some time during the course of the disease, usually from a few weeks to a few months after the onset, observations are made which indicate that the definite systemic disease is present. Arthritis, peripheral neuritis, evidence of involvement of the central nervous system, edema of an extremity, fibromyositis or even parotitis or orchitis may become apparent. Albumin and erythrocyturia may signify the onset of glomerulonephritis. Roentgenologic evidence of a thoracic lesion may be seen early in the course of the disease, or it may appear later and indicate that something is at hand other than a lesion localized in the upper part of the respiratory system.

Death is almost always caused by uremia, and may take place as rapidly as 10 days from the time of appearance of albuminuria and erythrocyturia.

OBSERVATIONS AT BIOPSY IN WEGENER'S GRANULOMATOSIS

Diagnosis of Wegener's granulomatosis is always difficult, particularly before the signs and symptoms of systemic disease have appeared. It would be very helpful if biopsy of a specimen of a suspicious lesion of the upper part of the respiratory tract would demonstrate vasculitis and indicate the true nature of the disease, but we have been unable to find a report in which biopsy did show definite vascular involvement. The table shows the results of biopsy in Wegener's granulomatosis as reported in the literature. Even when the specimen of tissue was from an extensively ulcerated nose or a mastoid process filled with abnormal tissue, microscopic examination demonstrated only inflammatory tissue or granulomas without signs of specificity.

Several authors[3,15,21] have found vasculitis in postmortem material taken from the upper part of the respiratory tract in instances of Wegener's granulomatosis (midline lethal granuloma), indicating that

TABLE I

BIOPSY OBSERVATIONS IN THE UPPER PART OF THE RESPIRATORY TRACT IN REPORTED CASES OF WEGENER'S GRANULOMATOSIS

CASES, NO., REFERENCE NO.	GROSS LESION	MICROSCOPIC APPEARANCE
1[8]	Widely ulcerated nasal mucosa	Granulation tissue, eosinophils, few giant cells
	Granular area of septum	Chronic inflammatory reaction
2[8]	Nasal mucosa ulcerated with crusts	Inflammatory reaction with lymphocytes
1[14]	Ulcer of nasal septum	Granulation tissue
1[15]	Granuloma of nasal septum	Granuloma with giant cells
2[15]	Granuloma of nasal septum	Nonspecific inflammation, some giant cells
1[16]	Granular nasal mucosa with much crusting	Granulation tissue with giant cells and eosinophils
1[17]	Acute mastoiditis	Chronic nonspecific inflammatory tissue
	Ulcerated, crusted nasal membrane	Granulation tissue with giant cells
1[18]	Granulation tissue	Granulation tissue with eosinophils
1[19]	Granular mass of septum	Simple granuloma
1[20]	Acute mastoiditis	Inflammatory tissue with eosinophils and giant cells
5[21]	Laryngeal stenosis	Chronic inflammatory tissue

perhaps more adequate biopsy at times might help in arrival at the proper diagnosis.

DIFFERENTIAL DIAGNOSIS

The most important differential distinction is between Wegener's granulomatosis (lethal midline granuloma) and reticulum-cell sarcoma. De Faria and associates[27] went so far as to say that all midline granulomas of the type under discussion are in fact instances of reticulum-cell sarcoma. The important differential point, however, is the development of periarteritis nodosa generally. In none of the cases

presented by de Faria and associates[27] was there pathologic evidence of periarteritis, and in none of the four patients in our series in whom postmortem examination was done was evidence of any type of malignant process found.

It is important to distinguish these lesions also from the indolent ulcerations produced by anaerobic streptococci and also from the specific granulomas, especially histoplasmosis, blastomycosis, tuberculosis, syphilis, yaws and the like.

NATURE OF PRESENT STUDY

The histories and pathologic findings in six cases of Wegener's granulomatosis (lethal midline granuloma) are presented. The first patient was alive and seemed well after 2 years with no treatment except the use of salicylates, at the time of this report. The other five patients died; postmortem examination was done in all but one.

REPORT OF CASES

CASE 1. A previously healthy 14-year-old girl began to experience attacks of an influenza-like syndrome in September, 1955. Muscle pains, headache, cough, hoarseness and fever accompanied each of the 15 or 20 attacks, which usually resolved after a few days' penicillin therapy. In February, 1958, persistent hoarseness led to biopsy of specimens of abnormal tissue in the subglottic area.

The hoarseness became increasingly severe and the patient was admitted to the Mayo Clinic in August, 1958. Indirect laryngoscopy demonstrated injected, edematous vocal cords and an obstructing mass, covered by a red crust, in the subglottic area. The intranasal structures appeared to be atrophic, and were covered with dry adherent crusts. Tracheotomy was carried out and specimens of tissue for biopsy were taken from the larynx, subglottic area and nose. Staphylococcus aureus was isolated, and the patient accordingly received erythromycin.

Results of an extensive general examination were negative except for slight elevation of the sedimentation rate, and albuminuria of grade 1 and erythrocyturia of grade 2. A definite diagnosis was not reached, and the patient was allowed to return home.

In January, 1959, pain and swelling in multiple joints, numbness of the right heel and lack of energy developed. The patient was examined again. The sedimentation rate was now 65 mm in one hour (Westergren) and albuminuria of grade 2 and erythrocyturia of grade 3 were recorded. At this time the larynx was essentially normal. An ulcer had developed on the tongue. Wegener's granulomatosis was suspected, and needle biopsy of a kidney was carried out. Since the general condition of the patient was relatively good, steroid therapy was withheld and she was allowed to go home with a prescription of salicylate therapy. At the time of this writing she was still living and attending school, more than 2 years after the first biopsy of laryngeal tissue. Symptoms referable to the joints were much abated. Varying grades of albuminuria and erythrocyturia persisted, however.

Histopathologic findings (Fig. 1) in various biopsies were:

1. Nose: nonspecific inflammatory reaction.

2. Larynx: ulceration with granulomatous inflammation of the base; poorly defined tubercles with giant cells.

3. Tongue: nonspecific inflammation.

4. Kidney: focal glomerulitis with possible arteritis.

Comment on Case 1. This is an instance of relatively mild Wegener's granulomatosis in which the laryngeal findings dominated the early and very confusing clinical picture. The laryngeal lesions abated considerably as the systemic disease appeared. Repeated infections of the upper part of the respiratory tract seem to have led to the genesis of inflammatory lesions in the nose and ulcerated granulomas in the larynx, and appear to have been important in the eventual development of very probable generalized periarteritis nodosa.

CASE 2. A 21-year-old man had severe nasal congestion in October, 1945. Two weeks later severe pain arose over the right maxilla and right upper teeth, and a copious bloody nasal discharge became prominent. Acute otitis media on the right became apparent. The nasal symptoms and facial pain continued in increasing severity, as did general malaise, and the patient was admitted to the Mayo Clinic in April, 1946.

Examination revealed a seriously ill patient with both nasal chambers filled with abnormal tissue which bled easily on manipulation

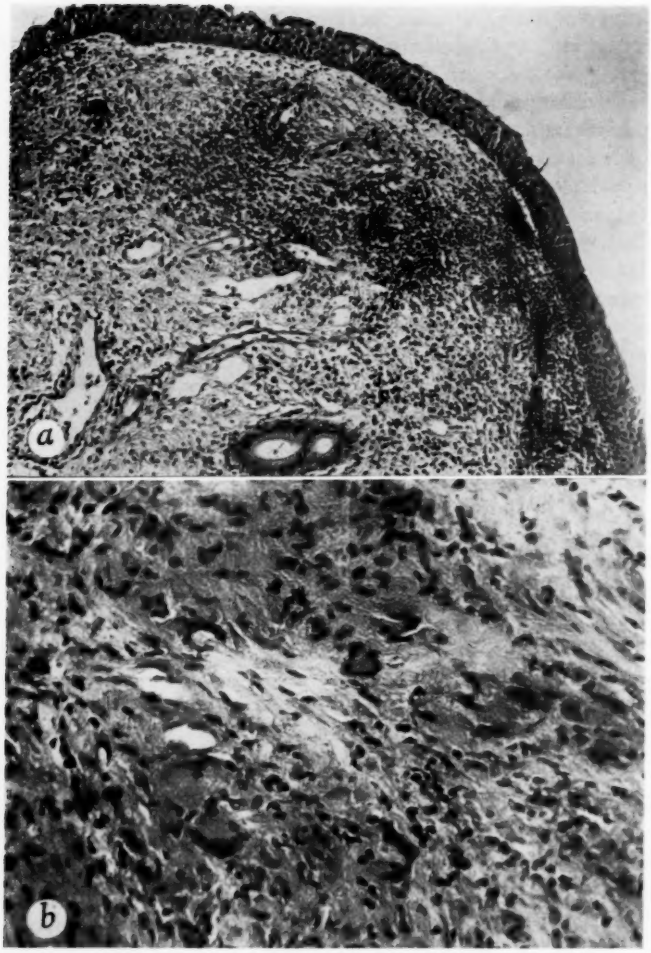


Fig. 1.—*a.* Nasal mucosa, showing nonspecific inflammatory reaction (hematoxylin and eosin; x100). *b.* Laryngeal biopsy. Note granulomatous inflammation with scattered giant cells (hematoxylin and eosin; x300).

and appeared to be malignant. A serosanguineous discharge was evident in the right external auditory canal. Roentgenograms showed the mastoid processes to be normal, but pansinusitis was present bilaterally. An extensive general examination demonstrated very little except anemia, leukocytosis, sedimentation rate of 110 mm in one hour (Westergren), erythrocyturia of grade 2 and albuminuria of grade 1 and axillary adenopathy. Intranasal surgical treatment was carried out and much abnormal tissue was removed from the nasal chambers and nasal septum. Pains in the joints, arms, legs and epigastrium developed. Periarteritis nodosa was suspected. Results of muscle biopsy were negative. In mid-May of 1946 ulcers developed on the patient's tongue, uvula and buccal mucous membrane, and roentgenograms disclosed congestion in the lower lobes of both lungs.

The patient died on May 26, 1946, about seven months from the onset of the respiratory symptoms. At the time of death the nose was filled with bloody scales and there was extensive destruction of the nasal septum.

Microscopic examination (Fig. 2*a* and *b*) of tissues taken from the nose showed granulomatous inflammation with poorly formed tubercles and scattered giant cells. Vasculitis was not evident.

Necropsy demonstrated periarteritis nodosa involving the lungs, liver, spleen and kidneys, with multiple infarcts.

Comment on Case 2. This case is an instance of Wegener's granulomatosis in which extensive granulomatous involvement of the nasal cavities dominated the picture in the upper part of the respiratory tract. The disease started as an apparently severe acute sinusitis, but soon systemic symptoms developed out of proportion to the nasal symptoms and signs and it became apparent that the disease process in the nose and ears was only one part of a widespread systemic disorder.

CASE 3. A 55-year-old man contracted an infection of the upper part of the respiratory tract in March, 1959. The infection did not abate and nasal polypi were removed a month later. Shortly after the operation bloody crusts began to form in the nose, and hearing became markedly impaired. Dyspnea developed at about the

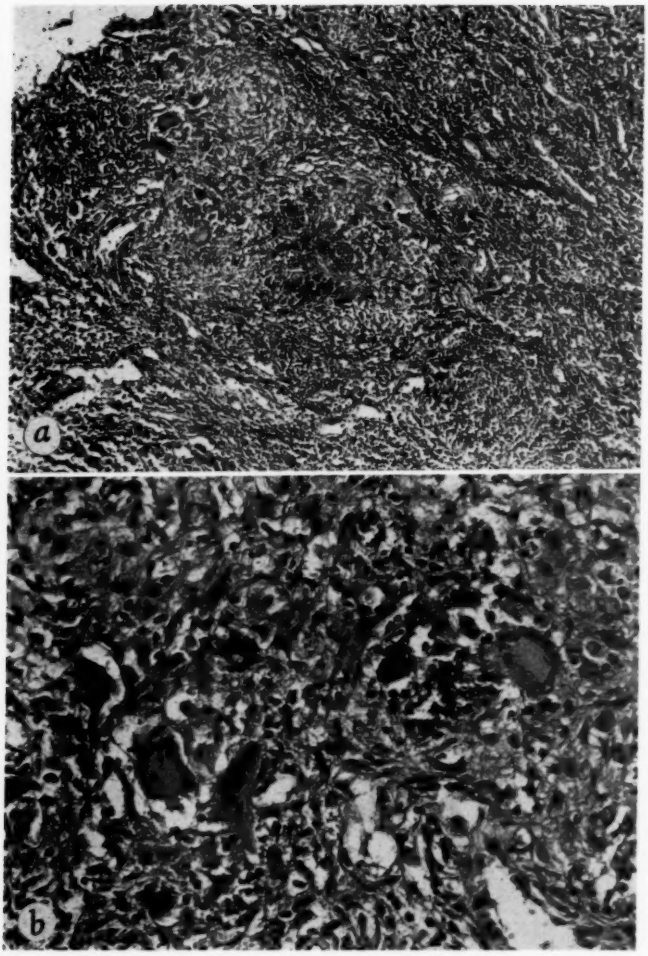


Fig. 2.—Wegener's granulomatosis. *a.* Low-power magnification of intranasal granuloma: note poorly formed tubercles with slight caseation and numerous giant cells (hematoxylin and eosin; x100). *b.* High-power magnification, showing prominent giant-cell reaction (hematoxylin and eosin; x300).

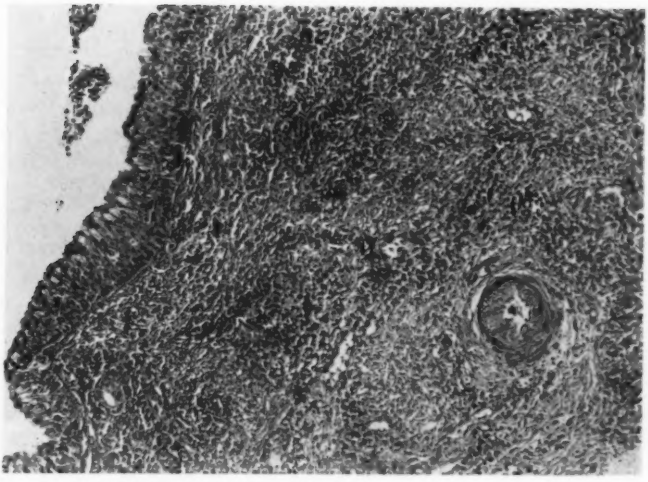


Fig. 3.—Nasal mucosa, showing marked nonspecific inflammatory reaction and obliterative change in one small artery (hematoxylin and eosin; x100).

same time, became progressively worse and was soon accompanied by hemoptysis.

At the time of admission of this patient to the Mayo Clinic on August 7, 1959, both nasal chambers were filled with large, odorous bloody crusts, removal of which left a granular, bleeding nasal membrane. Mild polypoid change of the vocal cords and some crusting in the subglottic area were noted. The tympanic membranes were thickened and there was fluid in the left middle ear. An audiogram showed a combined hearing loss of 85 decibels on the left and nerve deafness of 35 decibels on the right. Roentgenograms revealed thickened membranes in all the sinuses, sclerosis of the left mastoid process and indeterminate bilateral lesions in the thorax. Staphylococcus aureus and Streptococcus pyogenes were isolated from the nose. Albuminuria of grade 1 and erythrocyturia of grade 2 to 3 were consistently present, and the sedimentation rate was 113 mm in one hour (Westergren). Multiple biopsies of material from the nose showed

marked nonspecific inflammatory reactions with formation of granulation tissue (Fig. 3). Vasculitis was not seen.

Wegener's granulomatosis was suspected and steroid therapy was administered. The respiratory difficulty became progressively worse and the patient died on October 12, 1959, about 8 months after the onset of the initial upper respiratory infections. Postmortem examination demonstrated necrotizing granulomatous lesions of the lungs and spleen, associated with generalized periarteritis nodosa.

Comment on Case 3. The upper respiratory and thoracic lesions in this case appear to have developed at about the same time. Some degree of deafness on the right had been present before the onset of the patient's illness. The loss of hearing on the left was out of proportion to the inflammatory disease in the middle ear, and was of a neurosensory type, leading us to suspect that the loss of hearing may have been the result of vasculitis of the blood supply to the neural elements.

CASE 4. A 59-year-old man experienced marked nasal congestion, recurrent epistaxis, serosanguineous nasal discharge, severe facial pain, chills and fever in April, 1958. Unknown types of antibiotic agents were given. The symptoms did not abate and pain and swelling of the right lower leg developed.

The patient was admitted to the Mayo Clinic on April 28, 1958. The intranasal structures were found to be congested and the turbinates and septum were covered with small dry scales, removal of which left a raw bleeding surface. Roentgenograms of the sinuses showed nothing of significance. Multiple biopsies of material from the nose showed a marked nonspecific inflammatory reaction with formation of granulation tissue, some eosinophils (Fig. 4), but no vasculitis. Results of a general examination were negative except for indeterminate edema of the right leg and a sedimentation rate of 91 mm in one hour (Westergren). Staphylococcus aureus and Streptococcus pyogenes were isolated from the nose, and erythromycin was given. After some temporary regression of the nasal symptoms the formation of scales became more pronounced and a foul and bloody nasal discharge began. Hospitalization was necessary on July 8, 1958. Edema of the leg had increased and there were numbness, pain and tingling in both legs. Chills, fever, nausea and vomiting were prominent. Albuminuria of grade 2 and erythrocyturia of grade 3 were

Fig. 4.—Nasal mucosa: marked nonspecific inflammation with formation of granulation tissue. The inflammatory infiltrate consists of lymphocytes, plasma cells and numerous eosinophilic leukocytes (hematoxylin and eosin; x125).

recorded and the value for urea was 182 mg per 100 cc of blood. The sedimentation rate was 134 mm in one hour (Westergren) and roentgenograms revealed patchy pneumonitis of the right midlung. At this time the patient's nose was filled with bloody crusts, without definite ulceration of the underlying membrane. The patient died of uremia about four months from the onset of nasal symptoms.

Postmortem examination was not done. Although we were unable to demonstrate granulomatous lesions in the respiratory tract, the roentgenograms of the thorax disclosed a condition which was abnormal. The rapid course of the disease, the development of multiple systemic symptoms and the terminal uremia make a diagnosis of Wegener's granulomatosis very probable.

Comment on Case 4. This was an instance of Wegener's granulomatosis in which the intranasal lesions were relatively mild. Late in the disease the nose was filled with bloody crusts, but there was no

definite destruction of intranasal structures. For 3 months it appeared that we were treating a somewhat unusual and severe intranasal infection accompanied by an increased sedimentation rate and indeterminate swelling of the right leg.

CASE 5. A 52-year-old man had acute sinusitis and acute otitis media in May, 1953. The use of many antibiotic agents did not eradicate the infection, and in August, 1953, submucous resection and bilateral antral operations were necessary. After these procedures bloody crusts began to form in the nose, recurrent epistaxis arose and the hearing became progressively worse. In September, 1953, general malaise and weakness of the lower extremities developed. The sedimentation rate was 90 mm in one hour, and albumin and erythrocytes appeared in the urine.

The patient was admitted to the Mayo Clinic on October 21, 1953. The nasal chambers were seen to be filled with bloody crusts and there was a large septal perforation. The tympanic membranes were intact but were thickened, and had been invaded by blood vessels. There was marked loss of hearing bilaterally. Roentgenograms of the thorax were not significant. The value for urea was 320 mg per 100 cc of blood.

Periarteritis nodosa was suspected and cortisone was given. The patient died of uremia on November 2, 1953, about 6 months from the time of onset of the symptoms of infection of the upper part of the respiratory tract. Necropsy was reported as showing periarteritis nodosa with multiple infarcts of the kidney and spleen, and involvement of the hepatic capsule and intestinal arteries.

Intranasal biopsy was not carried out and granulomas of the lung were not demonstrated. The destructive process in the nose, the course of the disease and subsequent development of generalized periarteritis nodosa strongly favor a diagnosis of Wegener's granulomatosis.

CASE 6. Tinnitus and fullness developed in the ears of a 37-year-old housewife in January, 1952. Four weeks later her otologist was unable to find appreciable infection in the ears and inflated the eustachian tubes. Severe pains in the left cheek and left upper teeth soon developed, but again examinations of the ears, nose, throat and teeth did not explain the symptoms. In March, 1952, general malaise

and severe headache led to confinement of the patient in bed, and penicillin and chloramphenicol (chloromycetin) therapy was administered for 5 days. Swelling and pain in multiple joints developed on April 1, 1952. Two weeks later bilateral myringotomy relieved most of the patient's pain in the head.

The patient was admitted to the Mayo Clinic on May 12, 1952, because of general malaise, bilateral aural discharge and migratory pains in the joints. Examination demonstrated a small quantity of thin discharge in each external auditory canal and some loss of hearing in each ear. Roentgenograms revealed questionable chronic infection in both mastoid processes and diffuse infiltrations in both lungs. There were no symptoms in the thorax. Albuminuria and erythrocyturia were present. The sedimentation rate was 105 mm in one hour (Westergren). Rapid loss of hearing took place on May 17, 1952. Within 24 hours the patient was unable to hear a loud shout in the right ear, but she could repeat what she heard spoken in a loud voice in the left ear. The deafness was accompanied by vertigo, vomiting and spontaneous nystagmus to the left. There was very little drainage from the ears and roentgenograms of the mastoid processes showed considerable improvement. The cerebrospinal fluid was normal. The value for blood urea was elevated. It was felt that all the observations pertained to a generalized systemic disease. Results of muscle biopsy were negative. The patient died of uremia on June 3, 1952.

Postmortem examination demonstrated generalized periarteritis nodosa. There were granulomatous as well as vascular lesions in the lungs.

Comment on Case 6. Symptoms referable to the ears were prominent throughout this patient's illness, and for 3 months she complained only of tinnitus, fullness in the ears, malaise and facial and head pains. Late in the illness rapid increase in deafness and marked vertigo occurred, probably caused by vasculitis, since there did not seem to be sufficient involvement of the mastoid processes to explain the symptoms, particularly in view of the fact that the increase in deafness was bilateral.

COMMENT

On the basis of consideration of our own cases as well as a review of the literature, it seems evident that manifestations in the upper part

of the respiratory tract are an important part of Wegener's granulomatosis (midline lethal granuloma), and may be the only findings for weeks or months before the development of a thoracic lesion or other signs and symptoms suggesting more or less general systemic disease. In Case 1 laryngeal symptoms were presented for 6 months before the appearance of albuminuria and erythrocyturia suggested the possibility of something other than localized disease of the upper part of the respiratory tract, and it was 11 months before involvement of joints and numbness in one heel provided further evidence of systemic disease. In Cases 4 and 6 signs of systemic disease did not develop until 3 months from the onset of significant symptoms in the upper part of the respiratory tract. All patients had an elevated sedimentation rate, and the appearance of albuminuria and erythrocyturia was an early indication of systemic involvement.

Biopsy of tissue from a lesion in the upper part of the respiratory tract was done in four of six cases and vascular involvement was not detected. In Case 1 laryngeal biopsy demonstrated granulomatous inflammation, while microscopic examination of intranasal tissue demonstrated only a nonspecific inflammatory reaction. In Case 2 granulomas were seen deep in a very adequate specimen of tissue with only nonspecific inflammatory tissue on the surface, which suggests that biopsy should be more extensive when Wegener's granulomatosis is suspected.

Wegener's granulomatosis should be suspected when apparent and prolonged infection of the upper part of the respiratory tract does not respond to extensive treatment, and when lesions varying from granulation and congestion of the turbinates, which become covered with crusts, to extensive destructive granulomas appear in the respiratory tract.

Definite diagnosis cannot be made on the basis of observations in the respiratory tract alone, but depends on recognition of the development of more or less generalized periarteritis nodosa.

From the fact that evidence of generalized systemic involvement did not appear until weeks or months after the initial infection in the upper part of the respiratory tract in the majority of cases reported in the literature and in our own group of cases, it may be suspected that these patients became generally hypersensitive to an auto-antigen produced by the infection, as suggested by Kahn.[28]

SUMMARY

1. Six instances of Wegener's granulomatosis with prominent features referable to the upper part of the respiratory tract have been presented.

2. The nose, larynx or ears or all three structures may be involved in a given instance of the disease.

3. Results of biopsy of specimens of tissue from lesions in the upper part of the respiratory tract usually are inconclusive, and even when specimens are taken from extensively involved structures histopathologic examination does not lead to a definite diagnosis of Wegener's granulomatosis.

4. Wegener's granulomatosis is to be suspected when necrotizing granulomas or crust-covered granular lesions appear in the nose or larynx of a patient whose prolonged and severe apparent infection of the upper part of the respiratory tract has not responded to vigorous treatment.

5. Lesions of the upper part of the respiratory tract can be suggestive of Wegener's granulomatosis, but accompanying periarteritis nodosa must be recognized before a definite diagnosis can be made.

MAYO CLINIC

REFERENCES

1. Wegener: Über generalisierte, septiche Gefässerkrankungen. Verhandl. deutsch. Path. Gesellsch. 29:202-208, 1936.

2. Wegener, F.: Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und des Nieren. Beitr. path. Anat. allg. Path. 102: 36-68 (Jan. 5) 1939.

3. Plummer, N. S., Angel, J. H., Shaw, D. B., and Hinson, K. F.: Respiratory Granulomatosis with Polyarteritis Nodosa (Wegener's Syndrome). Thorax 12:57-64 (Mar.) 1957.

4. Milner, P. F.: Nasal Granuloma and Periarteritis Nodosa: Report of a Case. Brit. M. J. 2:1597-1599 (Dec. 31) 1955.

5. Weinberg, Tobias: Periarteritis Nodosa in Granuloma of Unknown Etiology: Report of Two Cases. Am. J. Clin. Path. 16:784-791 (Dec.) 1946.

6. Godman, G. C., and Churg, Jacob: Wegener's Granulomatosis: Pathology and Review of the Literature. A.M.A. Arch. Path. 58:533-553 (Dec.) 1954.

7. Blatt, I. M., Seltzer, H. S., Rubin, Philip, Furstenburg, A. C., Maxwell, J. H., and Schull, W. J.: Fatal Granulomatosis of the Respiratory Tract (Lethal Midline Granuloma-Wegener's Granulomatosis). A.M.A. Arch. Otolaryng. 70:707-749 (Dec.) 1959.

8. Stratton, H. J. M., Price, T. M. L., and Skelton, M. O.: Granuloma of the Nose and Periarteritis Nodosa. Brit. M. J. 1:127-130 (Jan. 17) 1953.

9. Atkins, J. P., and Eisman, S. H.: Wegener's Granulomatosis. Tr. Am. Laryng. A. 80:253-276, 1959.

10. Atkins, J. P., and Eisman, S. H.: Wegener's Granulomatosis. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 68:524-547 (June) 1959.

11. Wilson, K. S., and Alexander, H. L.: The Relationship of Periarteritis Nodosa to Bronchial Asthma and Other Forms of Human Hypersensitiveness. J. Lab. and Clin. Med. 30:195-203 (Mar.) 1945.

12. Goddard, J. W.: Granuloma, A Characteristic "Qualitative" Change in Focal Anaphylactic Inflammation. Am. J. Path. 23:943-965 (Nov.) 1947.

13. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity. Bull. Johns Hopkins Hosp. 72:65-88 (Feb.) 1943.

14. Walton, E. W., and Leggat, P. O.: Wegener's Granulomatosis. J. Clin. Path. 9:31-37 (Feb.) 1956.

15. Seidelin, R., and Willcox, A.: Giant-Cell Granulomata of the Mucous Membranes and Polyarteritis Nodosa. Arch. Middlesex Hosp. 4:171-181, 1954.

16. Howells, G. H., and Friedman, I.: Giant Cell Granuloma Associated with Lesions Resembling Polyarteritis Nodosa. J. Clin. Path. 3:220-229 (Aug.) 1950.

17. Herberts, G., Hillerdal, O., and Ranström, S.: Rhinitis, Sinusitis and Otitis as Initial Symptoms in Periarteritis Nodosa: (Wegener's Granulomatosis). Acta Otolaryng. 48:205-218, 1957.

18. Kelly, H. D. B.: Granuloma of the Nose and Necrotizing Arteriolitis. J. Laryng. and Otol. 70:313-316 (May) 1956.

19. McCallum, A. G.: Sinusitis, Granuloma of Nose and Periarteritis Nodosa. J. Laryng. and Otol. 68:560-567 (Aug.) 1954.

20. Rose, G. A., and Spencer, H.: Polyarteritis Nodosa. Quart. J. Med. n.s. 26: 43:81 (Jan.) 1957.

21. Fahey, J. L., Leonard, Edward, Churg, Jacob, and Godman, Gabriel: Wegener's Granulomatosis. Am. J. Med. 17:168-179 (Aug.) 1954.

22. Chomet, Bernhard, Pilz, C. G., Vosti, Kenneth, and Levine, Victor: Case of Wegener's Granulomatosis. A.M.A. Arch. Path. 66:100-107 (July) 1958.

23. Felson, Benjamin, and Braunstein, Herbert: Noninfectious Necrotizing Granulomatosis: Wegener's Syndrome, Lethal Granuloma, and Allergic Angiitis and Granulomatosis. Radiology 70:326-334 (Mar.) 1958.

24. Tuhy, J. E., Maurice, G. L., and Nelson, R. N.: Wegener's Granulomatosis. Am. J. Med. 25:638-646 (Oct.) 1958.

25. Hoch, C. W.: Wegener's Granulomatosis. A.M.A. Arch. Otolaryng. 63:120-123 (Feb.) 1956.

26. Levine, Howard, and Madden, T. J.: Wegener's Granulomatosis: Report of a Case. Am. Heart J. 53:632-637 (Apr.) 1957.

27. de Faria, J. L., Cutin, Moyses, and Morgante, Paulo: Malignant Granuloma of the Face: Contributions to Its Nosology. A.M.A. Arch. Otolaryng. 65:255-262 (Mar.) 1957.

28. Kahn, R. L.: Tissue Immunity—Its Possible Relationship to Midline Facial Granulomatous Ulceration. Univ. Michigan M. Bull. 20:208-218 (Aug.) 1954.

LXI

THE CEREBRAL CORTEX AND HEARING

LAMAR ROBERTS, M.D.
(by invitation)

GAINESVILLE, FLA.

An attempt will be made to evaluate the present status of knowledge about the role of the cerebral cortex in hearing. Peripheral mechanisms as well as subcortical nuclei and pathways will not be reviewed and will be considered only when necessary to clarify cortical representation. The data obtained from stimulation and ablation experiments in animals, particularly cat and monkey, will be summarized briefly. The anatomical and physiological studies in man will be given and discussion and summary will follow.

A. ANIMAL EXPERIMENTS

1. *Evoked Potentials.* A considerable amount of work has been done using pure tone and click stimulations as well as stimulation of auditory nerve fibers and recording of evoked potentials from the cortex. The majority of this work has been done in the cat. The terminology used here is taken from Rose and Woolsey.[1] In Figure 1 is seen the cortical region activated by sound stimuli in the deeply anesthetized cat. AI is the primary auditory area and corresponds quite closely to the cyto-architectonic typical primary sensory area (koniocortex). In AI the pattern of projection from the periphery seems to be an orderly one in that stimulation of the base of the cochlea evoked responses anteriorly while stimulation of the apex produced it posteriorly.

The reverse is true of the projection to the second auditory area. Stimulation of the apex of the cochlea produced responses anteriorly (the crossed hatched area in Figure 1); whereas, stimulation of the

From the Division of Neurosurgery of the University of Florida.

base evoked responses posteriorly (in the cross hatched and dotted part of Figure 1). The upper part of the posterior ectosylvian area (EP) is cytologically different from the primary auditory area and smaller potentials are seen here from cochlea stimulation. There has been some difference of opinion as to whether the inferior part of EP (the dotted and crossed hatch area in Figure 1) is a part of the auditory area, but from the evoked potential studies this seems to be clearly the posterior part of the second auditory area.

Kiang[2] has recorded from isolated patches of cortex and has found that responses occurred from a patch in AI, AII or EP when all other auditory cortex of the same side and all auditory cortex of the opposite hemisphere had been removed. This would seem to indicate that these responses are mediated through subcortical rather than cortical connections, i.e. there are subcortical connections with AII and EP as with AI. Kiang also confirmed earlier work that an evoked response may be recorded from ventral EP after application of strychnine to a small area of AI or anterior AII.

In January of this year Thompson and Sindberg[3] from Woolsey's laboratory extended considerably the cortical area from which responses may be obtained to click stimuli. Responses occurred from the sensori-motor area as well as from the anterior lateral and suprasylvian gyri. These responses occurred even after bilateral ablation of the auditory cortex considered above.

Lilly[4] has used a recording technique which gives simultaneous samples of electrical activity from 25 electrodes on the cerebral cortex. He has recorded the spontaneous activity as well as that following click stimuli. In both instances the "forms and figures" follow a definite repeatable pattern. The "forms and figures" described by Lilly show the electrical activity in the numerous electrodes at a given time and how this activity spreads in time. There was a clear difference between deep, light, and no anesthesia. A figure which starts in AI or AII may progress posteriorly with a leading edge velocity of 1 to 2 meters a second; at the junction with EP this edge slows to about 0.1 meter a second. The retreating edge velocity over the entire area is about 0.1 meter per second. The spontaneous figures usually arise in EP and they have an advancing and retreating edge of about 0.1 meter per second. There are also responses in the sensori-motor cortex to click stimulation.

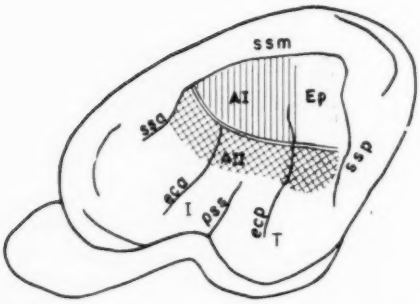


Fig. 1.—Cortical region activated by sound stimuli in deeply anesthetized cat. This figure is taken from Rose and Woolsey[1] and reproduced with permission of the University of Wisconsin Press.

In the monkey, Pribram et al[5] have shown the most extensive cortical responsive area to acoustic clicks. In contradistinction to the cat the primary auditory area in the monkey usually has been considered to be mostly in the supratemporal plane, i.e. within the sylvian fissure. The usual method of exposing this area has been to remove the parietal operculum. Pribram succeeded in teasing open the sylvian fissure and recording from the supratemporal plane, insula, and frontal and parietal opercula without cortical damage. Following click stimuli evoked potentials were recorded on the lateral surface as shown in Figure 2 and on the lateral surface as well as within the sylvian fissure as shown in Figure 3. Thus, it can be seen that the cortical response area to click stimuli in the monkey is quite similar to that in the cat.

2. *Cortical Stimulations.* Animals, of course, cannot communicate verbally to us what they hear; so that there are no reports comparable to those given below in man. The only cortical stimulation studies concerning movements of the ear are the ingenious experiments of John Lilly.[6] Lilly has implanted up to 610 electrodes covering approximately 19 square centimeters of cortex at about 1.5 to 2 millimeter intervals over one hemisphere. For stimulation he used symmetrical bi-directional pulse pairs instead of rectangular unidirectional pulses which were found injurious. In Figure 4 points of stimulation

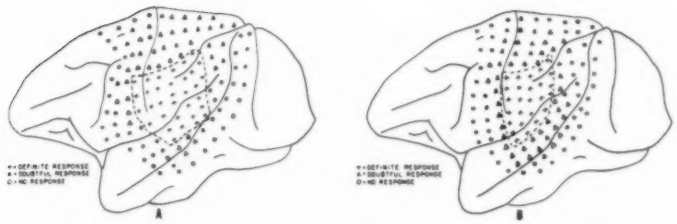


Fig. 2.—Extent of cortex from which observable potential deflections were recorded in two monkeys. This figure is taken from Pribram et al[5] and is reproduced with permission of Charles C. Thomas.

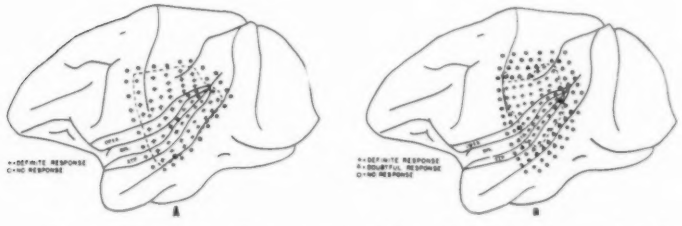


Fig. 3.—The extent of cortex activated by stimulation of contralateral (3a) and ipselateral (3b) ears. This figure is taken from Pribram et al[5] and reproduced with permission of Charles C. Thomas.

in the precentral gyrus and anteriorly (co-existent with what is usually considered the frontal eye field) and in the superior temporal region are seen which yielded movements of the ear. Sugar et al[7] have shown by the method of strychnine neuronography connections between the supratemporal plane of one hemisphere with that of the other as well as with the homolateral frontal "eye field" area and the anterior occipital region.

3. *Ablations.* It has been shown that the completely decorticate dog can acquire a conditioned response to sound although not as well as an intact animal. Most of the early work in this area was concerned with determining the intensity threshold of hearing for pure tones after various cortical ablations. It has been shown that absolute

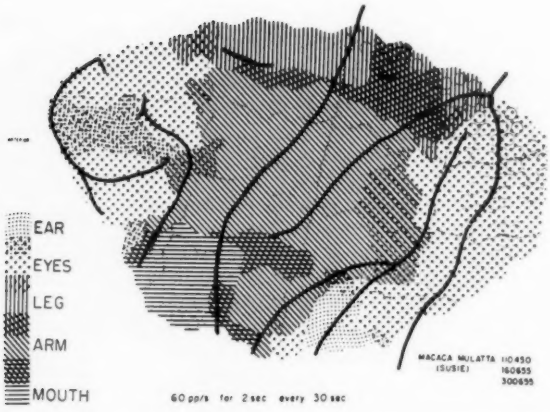


Fig. 4.—Map movements elicited at 60 pp/sec at threshold from the cortex of unanesthetized Macaca mulatta (610 electrodes). This figure is taken from Lilly[6] and reproduced with permission of the University of Wisconsin Press.

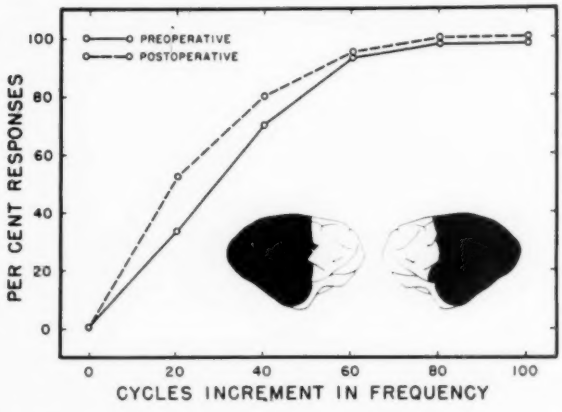


Fig. 5.—Massive extirpation of posterior cerebral cortex sparing somatic area 2. Capacity for frequency discrimination is retained, but extensive retraining is required. This figure is taken from Meyer and Woolsey[8] and reproduced with permission of Charles C. Thomas.

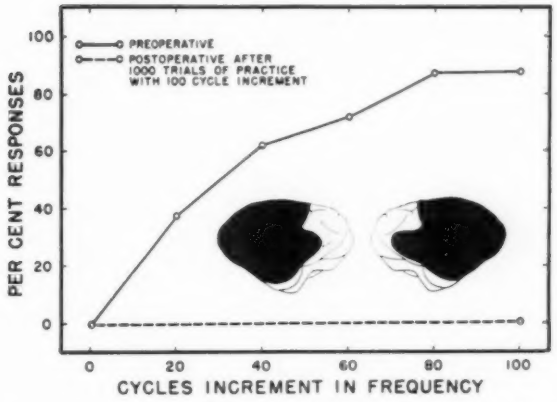


Fig. 6.—Massive extirpation of posterior cerebral cortex including entire auditory region. Postoperative there is no evidence for frequency discrimination within 50 sessions or 1,000 trials, nor for simple conditioning of a pure tone within 40 sessions or 800 trials. This figure is taken from Meyer and Woolsey[8] and reproduced with permission of Charles C. Thomas.

intensity threshold to pure tones does not rise appreciably following ablation of auditory cortex in the cat.

Meyer and Woolsey[8] trained cats to discrinimate small differences in the frequency of auditory stimuli. Figure 5 shows that the cat could relearn a frequency discrimination after removal of all auditory cortex except that of somatic area 2. However, if somatic area 2 is included (Fig. 6) then the frequency discrimination could not be acquired but discrimination of small changes in intensity could be. Neff[9-13] in a series of experiments has shown that after bilateral ablation of auditory areas 1, 2, and EP as well as somatic area 2 ability to discriminate changes in frequency was essentially unimpaired. There was an initial loss of the learning habits but all animals were able to relearn. In addition to the areas ablated by Neff, Meyer and Woolsey had removed most of the insula and temporal region as seen in Figure 7, taken from Harlow Ades' excellent article.[14]

Neff has trained cats to make a response requiring localization of sound in space. Figure 8 shows that cats with bilateral ablation

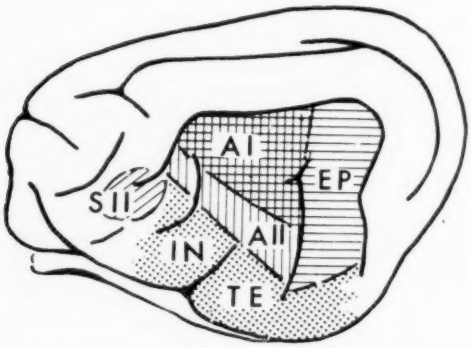


Fig. 7.—Composite view of all areas of cat brain showing auditory function. AI, first auditory area; AII, second auditory area; EP, posterior ectosylvian area; SII, second somatic area; IN, insula region, TE, temporal area. This figure is taken from Ades[14] and reproduced with permission of the American Physiological Society.

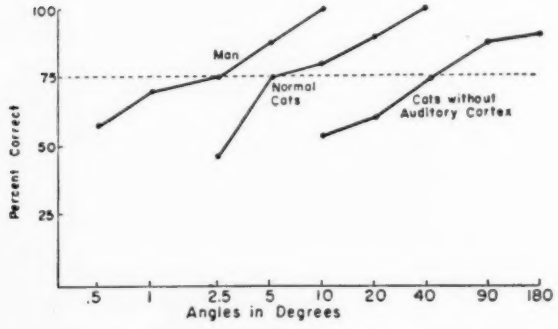


Fig. 8.—Curves showing angles discriminated correctly and sound localization by man, normal cats, and cats with auditory cortex ablated. The dotted line indicates the 75 per cent level. This figure is taken from Neff and Diamond[13] and reproduced with permission of the University of Wisconsin Press.

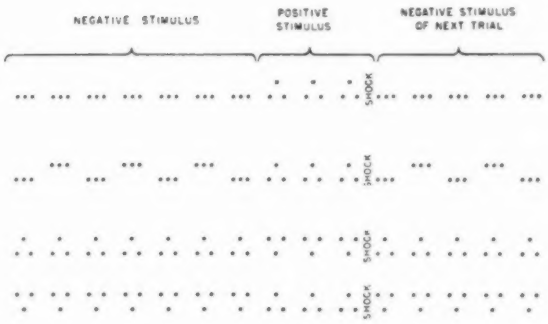


Diagram to show sequence of tones in testing discrimination of tonal patterns.

Fig. 9.—Diagram to show sequence of tones in testing discrimination of tonal patterns. This figure is taken from Neff and Diamond[13] and reproduced with permission of the University of Wisconsin Press.

of AI, AII, and EP were able to make discriminations only when the angle between successive positions of the buzzer was 40 degrees or more at a criterion of 75 per cent.

In other experiments by Neff and his collaborators, ability to discriminate patterns has been investigated. In Figure 9 the first line shows only a frequency discrimination whereas the others require that they be perceived as a group or pattern. Following bilateral ablation of AI, AII, and EP the frequency discrimination is maintained but the pattern discrimination cannot be relearned under the conditions described. In other experiments the temporal and insula region as seen in Figure 7 has been removed bilaterally with a profound loss in the ability to discriminate between groups of tones which differ only in temporal patterning (high-low-high vs. low-high-low).

Most of the preceding experiments have been accompanied by studies of degeneration of the thalamic nuclei. It seems from these studies that fibers from the medial geniculate go to the insula and temporal region as well as to AI, AII, EP, and SII.

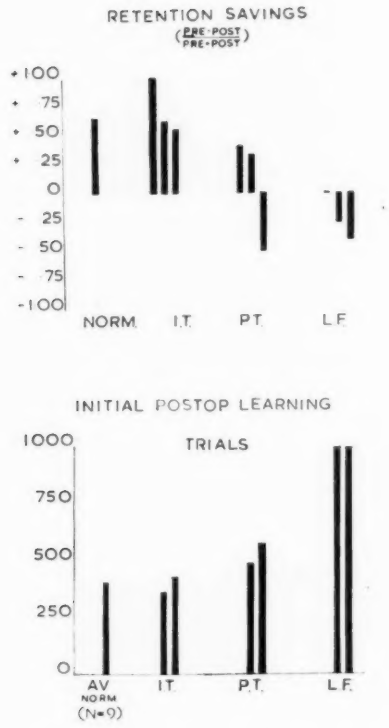


Fig. 10.—Pre-operative and postoperative learning of performance scores. This figure is taken from Weiskrantz and Mishkin[19] and reproduced with permission of MacMillan and Company, Limited.

Moore and Diamond[15] showed that after bilateral ablation of the hippocampus the cat lost the ability to avoid shock when preceded by the conditioned stimulus of a buzzer. Relearning occurred with 50 per cent saving. On the other hand after the same ablation a naive cat was able to learn the avoidance without difficulty. In another experiment Moore[16] found that when the conditioned stimulus was a flashing light this habit was not lost following bilateral hippocampal ablation. These experiments would seem to indicate that the hippo-

campus is involved in auditory learning but not in visual learning. This is one of the very few studies showing involvement of the hippocampus in complex auditory processes.

In the monkey Blum[17] has shown difficulty in the ability to discriminate a bell from a buzzer either immediately or after a delay following bilateral dorso-lateral frontal ablations.

Following biateral excision of the auditory area (as defined by Pribram et al[5]), Jerison and Neff[18] found that the monkey cannot make a pattern discrimination (800 - 1,000 - 800 vs. 1,000 - 800 - 1,000 cyles per second) but can make a frequency discrimination (800 - 800 - 800 vs. 800 - 1,000 - 800). This is the same type of loss as seen in the cat.

Weiskrantz and Mishkin[19] trained monkeys to discriminate a white noise from a pure tone of 1,000 cps. Following inferior temporal lesions there was no change in postoperative retention, or in new learning after operation. The subjects with superior temporal and adjacent parietal cortical lesions had slight difficulty in initial learning after operation and showed less than normal retention. Those animals with dorsolateral frontal ablations did not learn the problem initially after operation within 1,000 trials and had marked difficulty in relearning it when they had been trained before operation (Fig. 10). All removals were bilateral.

Morrell, Roberts, and Jasper[20] made epileptogenic lesions in monkeys by application of alumina gel discs. These monkeys had clinical seizures. When the alumina gel was applied to the superior temporal cortex or to the region of the amygdala the alpha rhythm could not be conditioned to auditory stimuli. Following excision of the cortex underlying the alumina gel as well as neighboring cortex the alpha rhythm could again be conditioned. It should be pointed out that the excision did not include the entire auditory cortex as outlined by Pribriam et al.

B. ANATOMICAL AND PHYSIOLOGICAL STUDIES IN MAN

1. *Stimulations.* During the course of operation for treatment of focal cerebral seizures, the exposed cerebral cortex has been stimulated while the patient is under local anesthesia (see Penfield and Ras-

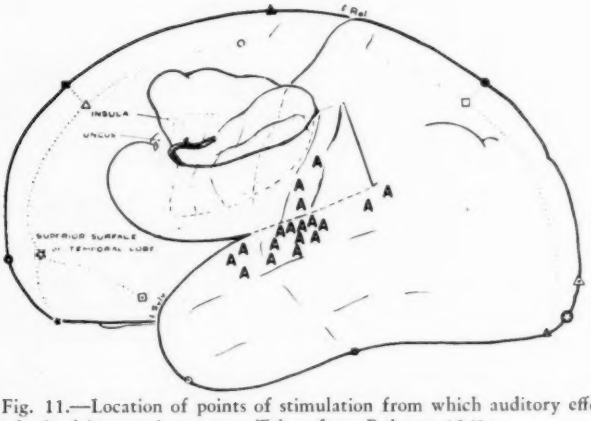


Fig. 11.—Location of points of stimulation from which auditory effects were obtained in conscious man. Taken from Roberts, 1960.

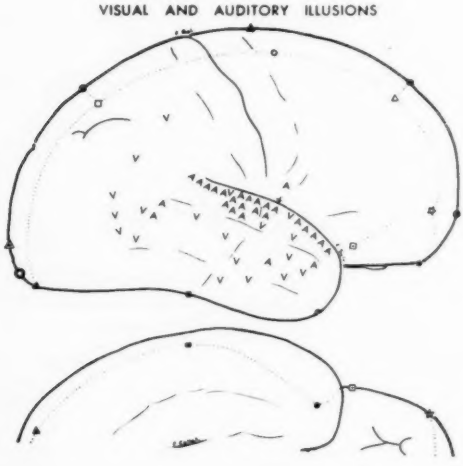


Fig. 12.—Location of points of stimulation producing visual and auditory illusions. Taken from Roberts, 1960.

mussen[21]). While working with Doctor Penfield I reviewed the stimulation results in 100 patients with seizures arising from one or the other temporal lobe. Figure 11 shows the auditory responses obtained in these patients (they are indicated on the left hemisphere though they occurred during stimulation of the right hemisphere as well). The patient would report buzzing, ringing, sound of a motor running, a bell, a whistle, sounds of a bird chirping, etc. Some of these sounds could be interpreted as pure tones and others as more complicated forms. The sounds were heard as coming from the contralateral ear or both ears.

The surgeon has also stimulated the cortex while the patient received various auditory stimuli, for example, the sounds of the operator's voice or a clock ticking. Some patients have reported changes in the sounds heard while the stimulating electrode was applied to the cortex (Fig. 12). These responses have been classified as auditory illusions. The sound may grow louder or softer; it may seem closer or farther away; it may build up in a crescendo with changes in quality or decrease; it may appear distorted or unusual. It is seen that the stimulations producing auditory illusions lie more superiorly in the temporal region as compared with the visual illusions.

More complicated sounds occurring during dream-like states and referred to as auditory hallucinations by Penfield are seen in Figure 13. These responses may be only auditory as for example a person's voice, perhaps remembered from a conversation in the past, or they may contain visual as well as auditory components.

Parenthetically, it should be mentioned that larbyrinthine responses have also been obtained from the superior temporal region (Fig. 14). These include a sensation of falling, rotation, or dizziness.

Penfield and Kristianson[23] have shown that the location of the epileptogenic lesion in patients with an auditory aura as the initial phenomenon in their seizures is in the superior temporal region.

Along a little different line of investigation, an electric current has been applied to cortical points while the patient has attempted to name a series of pictures of objects. The dysphasic or aphasic types of responses have been seen in the posterior temporal and parietal region as well as in Broca's area and the supplementary motor area of

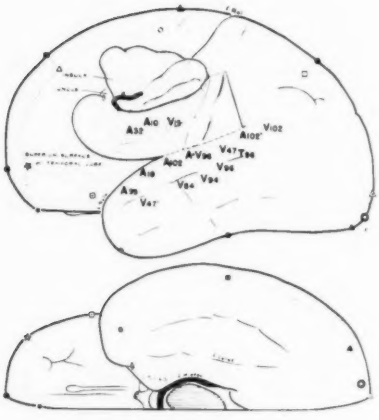


Fig. 13.—Location of points of stimulation producing auditory and visual hallucinations. Taken from Roberts, 1960.

the dominant hemisphere (Fig. 15). For details of this work the reader is referred to Penfield and Roberts.[24]

2. *Diseases and Excisions.* Precise localization of the cortical representation of hearing in man has not been worked out. In cases with cortical deafness the lesions have been large ones in the posterior temporal and adjacent parietal region bilaterally (see Penfield and Roberts[24]). When the patient has been found to be almost or completely deaf as a result of cortical destruction, no more accurate anatomical delineation of cortical auditory areas may be made than to say that it is the cortex surrounding the posterior end of the sylvian fissure.

It has been shown that following temporal lobectomy, consisting of the removal of the anterior five to seven centimeters and including Heschl's convolutions, that hearing is slightly decreased, more in high tone frequencies and more in the opposite ear. Sanchez-Long and Forster[25,26] have shown that localization of sound in space may be affected more in the contralateral ear with tumors of the temporal lobe and occasionally with frontal lobe tumors. Walsh[27] found that

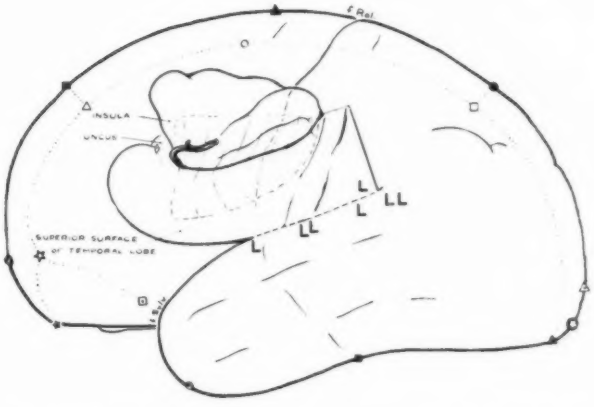


Fig. 14.—Location of points of stimulation where labyrinthine or vestibular responses occurred. Taken from Roberts, 1960.

the ability to localize sound in a vertical plane may be lost whilst localization in a horizontal plane remains possible.

It should be pointed out that numerous cases reported by Henschen[28] with lesions involving the dominant frontal lobe showed difficulty in the comprehension of auditory components of language as well as other dysphasic disturbances. Details are not available in these cases, however, as regards primary hearing as opposed to the more complicated aspects of understanding the spoken word.

C. COMMENT

No attempt has been made to give a complete review of all the work done in animals and man as regards the cerebral cortex and hearing. Much of the work given has been confirmed by other investigators. The selection of references was made according to the author's own interest and bias.

Most of the experimental studies have been carried out in the cat first and then extended to the monkey. It has been known for a long time that the auditory radiations extended to the ectosylvian gyrus

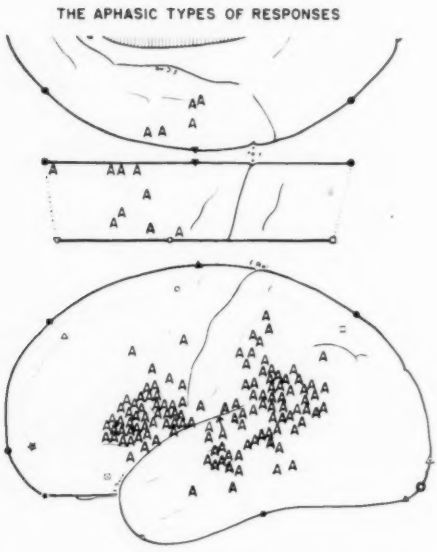


Fig. 15.—Location of points of stimulation where electrical interference produced dysphasia or aphasia. Taken from Penfield and Roberts, 1959.

in the cat and to the supratemporal plane in the monkey. These radiations are dissectible, and it was reasonable for attention to be focused on these cortical areas. For this reason it has taken longer to learn of the various cortical auditory areas other than the primary one. The experiments have been designed in such a way that territory at a distance from the superior temporal region has not been investigated —the exception to this is the recent studies involving the dorsolateral frontal area.

Pribram et al[5] have contended that areas other than the primary auditory area from which evoked potentials were obtained receive collaterals from the auditory radiation. If time were allowed for retrograde degeneration to occur in the thalamus, the evoked potentials could not be obtained. It has been found that thalamic degeneration following several cortical lesions may be less than that after one larger

lesion which includes no more than the combined smaller ones. This would indicate that the several areas receive thalamic fibers but few in number.

It would seem that we now have a better idea about the extent of the cortical auditory areas, but not necessarily the final one. Further studies are necessary to clarify the relationship of the frontal with the posterior areas from the anatomical standpoint. As suggested by Ades,[4] it would be extremely valuable to do evoked potential studies following the behavioral ones to determine if all auditory cortex had been excised, and to supplement this with thalamic degeneration determinations.

It seems obvious now that frequency discrimination is not bound in the cortex but in the medial geniculate. Sound localization and pattern discrimination are affected by cortical lesions. These are certainly more difficult than simple frequency discriminations. Other auditory parameters must be investigated. Some work has been done on the combination of auditory and visual stimuli, and this has to be extended.

In the organization and interpretation of these behavioral experiments, one should remember that the anatomical variables are not the only ones. False conclusions may be drawn from the anatomical standpoint, when in reality no conclusions were warranted (see the excellent critique by Meyer[29]).

Most of the time the human studies have lagged far behind animal experimentation. This is certainly true today as regards the cerebral cortex and hearing. Some of the techniques used in the laboratory can be carried over and used in man. We are now working on various auditory stimuli to be used during cortical stimulation of the locally anesthetized patient.

No mention has been made of the various theories of audition as none seems satisfactory, particularly when one reaches cortical levels of integration. Theories of auditory agnosia, especially when subdivided into verbal, literal, etc., are unsatisfactory. Proof of this last statement is given by Schuknecht and Woellner.[30] They demonstrated that two patients with acoustic neurinomas had abnormally poor speech discrimination as compared with pure tone thresholds in

the involved ears. This would be impossible if auditory verbal agnosia were only of cortical origin. Theories of hearing must take into consideration the types of defect seen in central as well as peripheral lesions, i.e. the disturbances which occur in auditory imperception (a term which I prefer to agnosia).

D. SUMMARY

1. A brief review has been given of the present status of knowledge about the cortical representation of hearing. Cat has been the animal most frequently used. Not only AI, AII, EP and SII but also the temporal and insular areas as well as the suprasylvian and anterior lateral gyri and part of the motor region seem to have auditory representation. Frequency discrimination is not cortically bound, but sound localization and pattern discrimination are affected by cortical lesions.

2. The results obtained in the cat have been confirmed in part in the monkey and to a considerably lesser extent in man.

3. Suggestions are given as regards future research.

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REFERENCES

1.Rose, J. E., and Woolsey, C. N.: Cortical Connections and Functional Organization of the Thalamic Auditory System of the Cat. Pp. 127-150 in: Harlow, H. F., and Woolsey, C. N., Eds. Biological and Biochemical Bases of Behavior. Madison, Wisconsin, University of Wisconsin Press, 1958.

2. Kiang, N.: Organization of Auditory Cortex in the Cat. Amer. J. Physiol. 183:635, 1956.

3. Thompson, R. F., and Sindberg, R. M.: Auditory Response Fields in Association and Motor Cortex of Cat. J. Neurophysiol. 23:87-105, 1960.

4. Lilly, J. C., and Cherry, R. B.: Surface Movements of Click Responses from Acoustic Cerebral Cortex of Cat: Leading and Trailing Edges of a Response Figure. J. Neurophysiol. 17:521-32, 1954.

5. Pribram, K. H., Rosner, B. S., and Rosenblith, W. A.: Electrical Responses to Acoustic Clicks in Monkey: Extent of Neocortex Activated. J. Neurophysiol. 17:336-44, 1954.

6. Lilly, J. C.: Correlations between Neurophysiological Activity in the Cortex and Short-term Behavior in the Monkey, pp. 83-100 in Harlow, H. F., and Woolsey, C. N., Eds., Biological and Biochemical Bases of Behavior. Madison, Wisconsin, University of Wisconsin Press, 1958.

7. Sugar, O., French, J. D., and Chusid, J. G.: Cortico-cortical Connections of the Superior Surface of the Temporal Operculum in the Monkey (Macaca mulatta). J. Neurophysiol. 1:175-84, 1948.

8. Meyer, D. R., and Woolsey, C. N.: Effects of Vocalized Cortical Destruction on Auditory Discriminative Conditioning in the Cat. J. Neurophysiol. 15:149-162, 1952.

9. Neff, W. D., Fisher, J. F., Diamond, I. T., and Yela, M.: Role of Auditory Cortex in Discrimination Requiring Localization of Sound and Space. J. Neurophysiol. 19:500-12, 1956.

10. Butler, R. A., Diamond, I. T., and Neff, W. D.: Role of Auditory Cortex in Discrimination of Changes in Frequency. J. Neurophysiol. 20:108-20, 1957.

11. Neff, W. D.: Behavioral Studies of Auditory Discrimination. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 66:106-14, 1957.

12. Goldberg, J. M., Diamond, I. T., and Neff, W. D.: Auditory Discrimination After Ablation of Temporal and Insula Cortex in Cat. Fed. Proc. 16:204, 1957.

13. Neff, W. D., and Diamond, I. T.: The Neural Basis of Auditory Discrimination, pp. 101-126 in: Harlow, H. F., and Woolsey, C. N., Eds. Biological and Biochemical Bases of Behavior. Madison, Wisconsin, University of Wisconsin Press, 1958.

14. Ades, H. W.: Central Auditory Mechanisms, pp. 585-613 in Field, J., Ed. Handbook of Physiology, Sec. 1, Neurophysiology, Vol. 1, American Physiological Society, Washington, D.C., 1959.

15. More, R. Y., and Diamond, I. T.: The Effect of Hippocampal Ablation on Conditioned Avoidance Behavior in the Cat. Paper read at Midwestern Psychological Association Meeting, 1957.

16. Moore, R. Y., Harvey, J. A., and Diamond, I. T.: Further Effects of Hippocampbale Ablation on Conditioned Avoidance Behavior in the Cat. Paper read at Midwestern Psychological Association Meeting, 1957.

17. Blum, R. A.: Effects of Subtotal Lesions of Frontal Granular Cortex on Delayed Reaction in Monkeys. A.M.A. Arch. Neurol. Psychiat. 67:375-86, 1952.

18. Jerison, H. J., and Neff, W. D.: Effect of Cortical Ablation in the Monkey on Discrimination of Auditory Patterns. Fed. Proc. 12:73-74, 1953.

19. Weiskrantz, L., and Mishkin, M.: Effects of Temporal and Frontal Cortical Lesions on Auditory Discrimination in Monkeys. Brain 81:406-14, 1958.

20. Morrell, F., Roberts, L., and Jaspeh, H. H.: Effect of Focal Epileptogenic Lesions and Their Ablation upon Conditioned Electrical Responses of the Brain in the Monkey. EEG Clin. Neurophysiol. 8:217-236, 1956.

21. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man. New York, MacMillan Company, p. 235, 1950.

22. Roberts, L.: Activation and Interferences Produced by Electrical Stimulation of the Brain in Conscious Man. Symposium on Brain Stimulation. Univ. of Texas Press, Austin, Texas. Sheer, D., Ed. 1960, in press.

23. Penfield, W., and Kristianson, K.: Epilepsy Seizure Patterns. Springfield, Ill., Charles C. Thomas, p. 104, 1951.

24. Penfield, W., and Roberts, L.: Speech and Brain Mechanisms. Princeton University Press, Princeton, N. J., p. 286, 1959.

25. Sanchez-Longo, L. P., Forster, F. M., and Auth, T. L.: A Clinical Test for Sound Localization and Its Applications. Neurology 7:655-663, 1957.

26. Sanchez-Longo, L. P., and Forster, F. M.: Clinical Significance of Impairment of Sound Localization. Neurology 8:119-125, 1958.

27. Walsh, E. G.: An Investigation of Sound Localization in Patients with Neurological Abnormalities. Brain 80:222-250, 1957.

28. Henschen, S. E.: Klinische und Anatomische Beitrage zur Pathologie des Gehirns. Stockholm, Nordiska Bokhandeln, Vol. 5, Vol. 6, Henschen, Vol. 7, 1920-1922.

29. Meyer, D. R.: Some Psychological Determinants of Sparing and Loss Following Damage to the Brain, pp. 173-192 in: Harlow, H. F., and Woolsey, C. N., Eds. Biological and Biochemical Bases of Behavior. Madison, Wisconsin, University of Wisconsin Press, 1958.

30. Schuknecht, H. F., and Woellner, R. C.: An Experimental and Clinical Study of Deafness from Lesions of the Cochlear Nerve. J. Laryngol. and Otol. 69:75-97, 1955.

LXII

THE PAROTID GLAND IN MIKULICZ DISEASE AND SJOGREN'S SYNDROME

WILLIAM GARTH HEMENWAY, M.D.

CHICAGO, ILL.

Mikulicz's name has been associated with parotid disease for many years. Most physicians are aware of this but few have a clear understanding of the actual disease processes involved. In 1888 Mikulicz presented a unique case before a medical meeting in Koeningsberg. A 42 year old man had developed bilateral lacrimal, parotid and submaxillary swellings. He published the case in 1892 and considered the disease to be a low grade infective process hitherto undescribed. Histologic examination of surgical specimens from the lacrimal and submaxillary glands disclosed atrophy of the parenchyma and diffuse replacement by lymphoid tissue. Unfortunately, the exact diagnosis in this case will always remain a mystery as insufficient information is available to assess the findings in the light of present day pathological knowledge.

A great deal of confusion about salivary and lacrimal gland swellings followed Mikulicz' report. Schaffer and Jacobson[1] in 1927 clarified the situation by classifying cases into Mikulicz disease and Mikulicz syndrome. Mikulicz disease was thought to be a low grade infection of unknown type running a slow course but eventually subsiding. Mikulicz syndrome included known diseases such as lymphomas, tuberculosis, syphilis, Boeck's sarcoid and toxic reactions to lead and iodides. This classification is widely followed today.

Only Mikulicz disease as it occurs in the parotid gland will be discussed in this report.

Godwin[2] in 1952 published a paper entitled "Benign Lymphoepithelial Lesion of the Parotid Gland." Pathological findings were

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From the Section of Otolaryngology of the University of Chicago.

presented in 11 cases. Although the exact nature of the lesion was unknown he considered it to be an inflammation. The process occurred in scattered foci, diffusely involving the entire gland or localized as a single mass with or without a capsule. Lesions consisted of a mass of lymphoid tissue containing scattered foci of epithelial cells that were traceable to duct origin. There was a variable degree of acinar destruction. Although lymphoid tissue was abundant it was evident that the lesion was not a malignant lymphoma. The epithelium varied from well differentiated tubular epithelium to solid foci of closely packed cells. Occasionally cysts lined with metapastic epithelium were seen. Grossly, the disease appeared as a well circumscribed mass or as a diffuse process involving part or all of the gland. Symptoms were minimal, and enlarged gland was usually the only presenting complaint. Middle aged females were commonly affected. No case showed lacrimal involvement or subsequently developed malignant disease. The lesion was usually unilateral but the other side occasionally become involved later. Godwin proposed the name "Benign Lymphoepithelial Lesion" for the condition. He stated that the lesion was identical with that which had been called Mikulicz disease and recommended that the eponym be dropped. He classified it along with Warthin's tumor under the term adenolymphoma.

Morgan and Castleman[3] in 1953 presented a clinicopathological study of Mikulicz disease. The gross appearance that was of a diffusely enlarged gland with preservation of the architecture. Microscopically there was replacement of the acinar parenchyma by lymphoid tissue and an intraductal proliferation of two cell elements; epithelial and myo-epithelial. This resulted in the formation of epimyoepithelial islands when the lumen of the duct was obliterated. They believed that the primary lesion was in the duct system and stated that the epi-myoepithelial islands were specific for the disease. The etiology was obscure.

Morgan[4] states that Mikulicz disease is commonly confined to the salivary glands, usually the parotid. It is rare in the lacrimal glands. He found the parotids showed identical pathological changes in Mikulick disease and Sjogren's syndrome and concluded that Mikulicz disease was a localized form of Sjogren's syndrome.

Patey and Thakray[5] in 1955 reported on studies based on surgical specimens. They described an uncommon and not too well recognized

inflammatory lesion of the parotid which was usually unilateral. A swelling developed in one parotid which gradually increased in size. This type was clinically and even pathologically difficult to distinguish from a tumor. Clinically they divided the cases into a diffuse form (inflammatory - obstructive) and a localized (tumor simulating) form. Their paper dealt with nine patients on whom total or partial parotidectomy was carried out. Careful study of the specimens showed that they were dealing with different degrees and manifestations of the same pathological lesion which they considered to be a chronic inflammatory process. Of the nine cases two were male and seven were female. Three cases were inflammatory obstructive, four were tumor simulating and two were intermediate forms. Sialographic findings were described in detail. The most characteristic x-ray finding was sialectasis. The main ducts were not usually involved and the typical picture was a glandular sialectasis. From serial sections of their material they concluded that the sialectatic picture was not due to filling of dilated ducts but to interstitial extravasation of lipiodal. This would explain why the lipiodal remains in the gland for weeks to even years after the injection. They concluded that these radiological findings are common to all types of chronic parotitis irrespective of the clinical picture and they may be occasionally found without clinical evidence of infection. Pathological findings are thoroughly described. They may be summarized as a progressive accumulation of lymphoid tissue around the intralobular ducts with associated hyperplasia and metaplasia of the ductal epithelium. The glandular elements atrophy and were replaced by lymphoid tissue. The larger intralobular ducts were mainly affected. The interlobular ducts showed only minor changes. The intralobular ducts became occluded with hyperplastic cells and the distal acini atrophy and were replaced by lymphoid tissue. The epithelial islands described were cross sections of solid intralobular ducts. These may undergo hyaline degeneration. They described clear spaces caused by extravasated lipiodal near the ducts if a recent sialogram had been performed. If a sialogram had been done sometime previously the pools of oily material would be surrounded by macrophages and foreign body giant cells. Eventually a dense fibrosis occurred. They summarized by stating that in this type of parotid disease there were two modes of presentation which may be described as inflammatory obstructive and tumor simulating. In both the pathological picture was one of chronic inflammation differing in degree and distribution. In both the radiological picture was that of glandular sialectasis. They recommended

conservative parotidectomy for the tumor simulating type and for the inflammatory obstructive type when severe clinical symptoms could not be controlled by conservative treatment.

Freund and Jonassen[6] described this disease under the name of benign lymphoepithelial disease. They postulated that the lesion arises from the parotid lymph nodes which normally contain ductal structures. Treatment proposed was excision of localized forms of radiation therapy for diffuse involvement.

Kay[7] described four lesions limited to the salivary glands in which the pathology was the same as that described by Godwin.[2] He concluded that the process was not systemic but confined to the salivary glands.

Orloff[8] grouped Warthin's tumor and Mikulicz disease under the heading of benign epitheliolymphoid lesions of the parotid gland. Mikulicz disease was often confined to one or both parotids and it was important for the surgeon to understand the nature of this benign self limited disease. Seventy-six per cent of 35 cases were female. Symptoms were minimal. The common complaint was a disfiguring mass which might fluctuate in size. The physical findings were of little help in distinguishing this lesion from other parotid diseases. Most commonly a diffuse swelling of the entire gland was noted but a circumscribed mass, either fixed or movable, may be present. In three cases x-rays revealed multiple small calcifications. Sialograms showed sialectasis in three of the four patients who had this examination. The gross appearance of the lesion usually showed preservation of the lobular pattern. The cut surface is smooth, resembling lymphoid tissue. There may be cystic spaces and small calcareous bodies. Microscopically the description conforms to that already described.[2-5] He concluded that this is an obscure type of chronic inflammatory disease which may continue for years without affecting the general health. He recommended surgical removal of localized lesions and x-ray therapy to diffuse lesions.

DuPlessis[9] found only three cases of Mikulicz disease in over 200 patients with parotid swellings. All three were in females. The average age was 35. The history was one of slowly progressive enlargement in one or both parotids. The process may be diffuse or localized. Stensen's duct orifice and the saliva were always normal. In the

advanced stages very little saliva was secreted but the patient should not complain of a dry mouth as the remaining major and minor salivary glands will keep it moist. Du Plessis stated that the earliest findings were an inflammation and fibrosis of the trabeculae between the lobules. Later the process spread to the gland parenchyma. Lymphoid infiltration commenced around the infralobular ducts. The epithelial and myoepithelial cells in these ducts proliferated and eventually filled the lumen of the duct thus forming solid cords. These appeared like islands on the microscopic section and sometimes underwent hyaline degeneration. The acini atrophied behind the obstructed cuts and were replaced by a diffuse lymphocytic infiltration. Sialographic findings were reviewed. The classical appearance was sialectasis which was usually assumed to be due to pooling of contrast material in dilated ducts but was actually the result of extravasation of the dye into the interstitial tissue through the weakened cut wall. Although the pathology in the parotid and sialographic pictures are similar in both Mikulicz and Sjogren's he did not feel they are otherwise related diseases. He felt that the parotid gland in Sjogren's underwent a primary atrophy with resultant diminution of salivary flow and increased likelihood of an ascending infection. He concluded that this pathological picture of proliferation of duct epithelium, lymphocytic infiltration, acinar atrophy and fibrosis was not pathognomonic of any disease but was a non-specific reaction of the parotid to chronic irritation. Mikulicz disease and Sjogren's syndrome must be differentiated on clinical grounds. He recommended that the name Mikulicz disease should be dropped and replaced by the term idiopathic chronic parotitis.

Bernier and Bhaskar[10] presented an extensive review of lympho-epithelial lesions of the parotid glands in 1958. They included cystic lymph nodes (benign lympho-epithelial cysts), Warthin's tumor (papillary cystadenoma lymphomatosum) mixed tumor in lymph nodes and benign lympho-epithelial lesion. There were 30 cases of benign lymphoepithelial lesions. They concluded that Mikulicz disease was primarily a lesion of the parotid lymph nodes which involved the parotid gland incidentally and represented a reactive hyperplasia of lymphatic tissue. A nodular type limited to the node and a diffuse type which infiltrates the parenchyma were described. The two types had a different microscopic picture. In the nodular type there was a diffuse lymphoid infiltration. Epithelial elements which were absent altogether or recognizable as widely isolated islands resembling glandu-

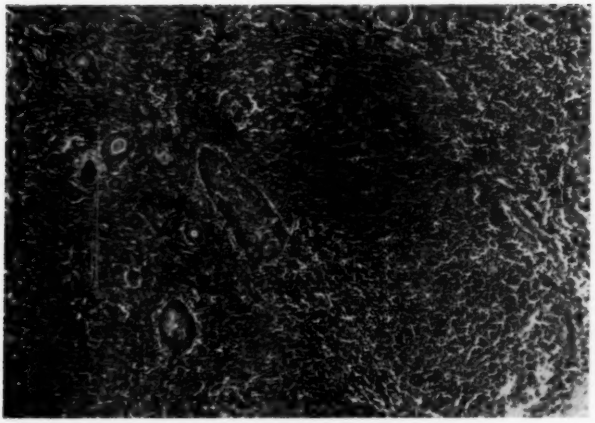

Fig. 1.—Case one. Histopathology of a localized mass in the parotid showing typical island formation, gross lymphoid infiltration and absence of acini.

lar tissue. Apparently they found no typical islands in this type. The diffuse type showed proliferating lymphoid tissue while the ducts had undergone squamous metaplasia and cyst formation.

Maxwell[11] recently presented an excellent description of this lesion.

Four cases of Mikulicz disease of the parotid gland are reviewed.

CASE 1. D.S. No. 587689. This 40 year old white man had a small mass 1 cm in diameter posterior to the angle of the mandible. He was otherwise in good health. At surgery the mass was found to be in the parotid gland and was excised. Histological study (Fig. 1) shows typical epithelial islands, chronic lymphatic infiltration and marked disappearance of the acini. A pathological diagnosis of solid adenolymphoma was made. This lesion could be called Mikulicz disease or the localized or tumor simulating type of chronic parotitis as described by Patey and Thakray.[5]

CASE 2. G.B. No. 650792. A lump in the left parotid area had been noticed for three weeks by this 59 year old white man. The

Fig. 2.—Case three. Sialogram showing sialectasis in a bilateral case of Mikulicz disease.

mass was about 1 cm in diameter, freely movable and situated just posterior to the angle of the mandible. The lump was excised under local anesthesia. A pathological diagnosis of solid adenolymphoma was made. The findings are typical of Mikulicz disease.

CASE 3. D.G. No. 295220. This 35 year old white woman was in the hospital in 1950 for treatment of obstructive jaundice. She had bilateral diffuse swellings of both parotids, more marked on the right. There were no symptoms or signs pointing to Sjogren's disease. X-rays showed multiple small calculi bilaterally. A sialogram was made on the right side (Fig. 2) and revealed moderate advanced sialectasis. No biopsy was done. Clinically this would seem to be a case of bilateral Mikulicz disease of the diffuse type.

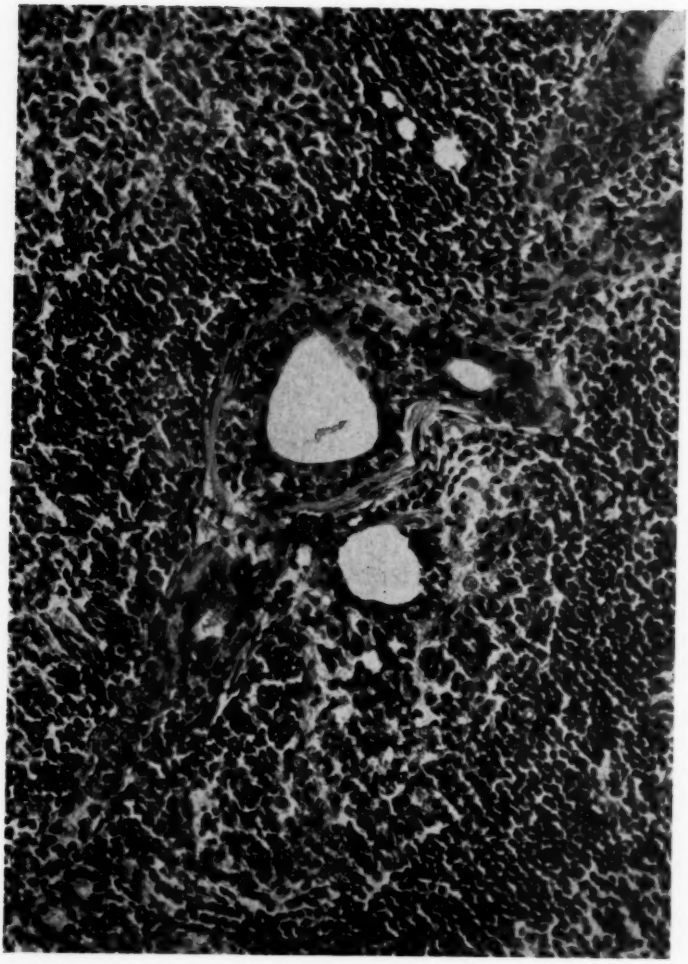

Fig. 3.—Case four. An early case of Mikulicz disease showing disappearance of the acini, lymphoid infiltration and metaplasia and dilatation of the intralobular ducts.

CASE 4. J.P. No. 668878. Mrs. J. P. was a 55 year old white woman who had a diffuse painless swelling of the left parotid gland of three weeks' duration. A sialogram showed early terminal sialectasis. A biopsy (Fig. 3) showed acinar destruction and lymphoid infiltration. The epithelium of the intralobular ducts was hyperplastic and the ducts were somewhat dilated. This was considered to be an early case of Mikulicz disease.

SJOGREN'S SYNDROME

Sjogren's Syndrome is generally considered to be a clinical entity of unknown etiology. Gougerot[12] in 1926 and Houwer[13] in 1927 reported frequent association of kerato-conjunctivitis sicca and rheumatoid arthritis but Sjogren[14] in 1933 published a full description of the condition. The disease occurs in women 86 to 95% of the time. The fully developed syndrome consists of:

1. Kerato conjunctivitis sicca,

2. Xerosotomia,

3. Pharyngitis, laryngitis, and rhinitis sicca,

4. Swelling of the parotid glands (a review of 19 autopsied cases showed parotid enlargement in eight),[17]

5. About two-thirds of cases have a polyarthritis closely resembling, if not identical with, rheumatoid arthritis.

By no means all cases develop the full clinical picture. Keratoconjunctivitis sicca, xerostoma, rheumatoid arthritis and parotid involvement are the common components. Any two of these occurring in a patient is usually sufficient for a diagnosis.

Morgan and Raven in 1952[15] called attention to the non-ocular findings in Sjogren's Syndrome. They summarized pathological findings in the parotid as consisting of epithelial atrophy with replacement by a large number of round cells and ultimately fibrosis. They stated that the earliest stage is a true lymphocytic infiltration of the parenchyma. As this becomes more marked while the secreting cells undergo atrophy with shrinking of the cytoplasm and condensation into

irregularly shaped masses showing squamous metaplasia. In the end stages only lymphoid tissue and condensed darkly staining epithelial clumps were left (Fig. 6). The ducts were surrounded by a zone of lymphoid tissue or by dense fibrosis. Similar changes were seen in the other major salivary glands and in the lacrimal gland which was never clinically enlarged.

Gurling[16] reported two female patients combining the features of Sjogren's disease with Felty's syndrome (rheumatoid arthritis, splenomegaly, leucopenia, anemia, skin pigmentation and lymphadenopathy).

In 1954 Cardell and Gurling[17] reported three cases with autopsy findings. They described two main pathological components, an atrophy of the salivary and lacrimal glands with associated mucosal dryness and rheumatoid arthritis. In the parotid earlier lesions showed two main features: a lymphoid infiltration which produced glandular enlargement and a parenchymal atrophy which resulted in impaired function. Both aspects showed slow progression and eventually both parenchyma and cellular infiltrate disappear and are replaced by adipose tissue. The histological picture was not one of an infective process although a secondary suppurative process may occur. For the present they placed Sjogren's syndrome into the ill-defined group of Collagen diseases.

MacLean and Robinson[18] reported LE cells in the peripheral blood of a patient with Sjogren's syndrome.

Coverdale[19] from a clinical analysis of over 200 cases of Sjogren's syndrome concluded that the clinical picture develops much earlier than is generally believed and that the disease is a manifestation of a constitutional defect.

McLenachan[20] reviewed 45 cases of Sjogren's syndrome. He found evidence of liver dysfunction in the majority of cases and postulates that the pathology is due to an inability of diseased liver to utilize vitamin A.

Heaton[21] states that Sjogren's syndrome and Systemic Lupus Erythematosis are manifestations of the same disease.

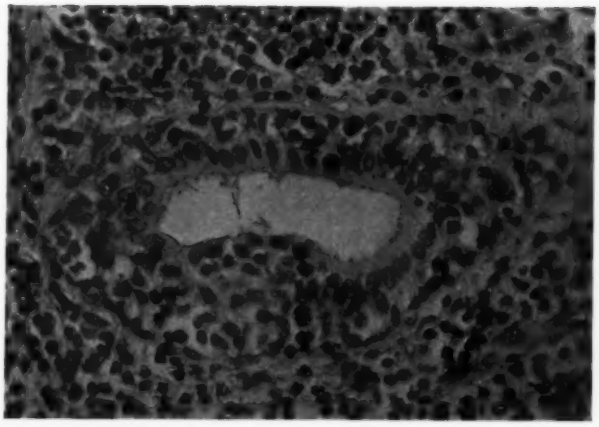

Fig. 4.—Case five. High power of the intralobular duct showing localized hyperplasia of the epithelial and myoepithelial cells.

Seven cases will be presented in which a clinical diagnosis of Sjogren's syndrome had been made and tissue from the parotid gland is available.

CASE 5. L.H. No. 260198. This 40 year old white female was seen on April 2, 1958. She presented with bilateral parotid swelling of about four months' duration. After the onset of the swelling she ran a fever of about one hundred and one degrees for four or five days. The amount of swelling had varied every two or three days. She had many complaints suspicious of a collagen disease. A diagnosis of lupus erythematosis had been entertained but ruled out by the medical department. A diagnosis of keratoconjunctivitis sicca had been made in 1956 and the patient had been using artificial tears daily. The mouth appeared moist and there was no evidence of arthritis. Sialograms showed bilateral terminal sialectasis. A biopsy of the right parotid gland was done and showed foci of lymphoid infiltration with destruction of the acini and early localized hyperplasia of the epithelium of the intralobular duct. The surrounding gland appeared healthy except that the cells contain few zymogen granules and superficially resemble a mucous gland. Figure 4 is a high power photomicrograph

Fig. 5.—Case six. Sialogram showing minimal terminal sialectasis.

showing early hyperplastic changes in the duct. We consider this to represent a very early lesion of the intralobular duct in Sjogren's disease. It would seem reasonable that this hyperplasia would eventually result in obliteration of the lumen and the formation of an epithelial island on sectioning.

CASE 6. A.W. No. 692498. Rheumatoid arthritis and keratoconjunctivitis sicca had been present in this 58 year old white female for several years. Bilateral painless parotid enlargement had been noted for five months. A sialogram showed early sialectasis (Fig. 5). Parotid biopsy showed a focus of lymphoid infiltration with hyperplasia of the epithelial cells of an intralobular duct. The lumen of the duct was about half obliterated and early hyaline degeneration was present.

CASE 7. B.P. No. 652496. This white woman was 34 years of age when first seen. She complained of dry mouth for four years and

dry eyes for two years. The right parotid had been swollen for one year and the left for four months. The left parotid was biopsied under local anesthesia. The acini were almost completely replaced by lymphoid cells. The ductal epithelium was hyperpastic forming many myoepithelial islands.

CASE 8. A.K. No. 542588. This 30 year old white woman was seen on February 13, 1952. A history of intermittent bilateral swelling of the parotids for four years was obtained. Usually only one side at a time would be enlarged. When examined, both glands were diffusely enlarged, firm and non-tender. The left parotid was biopsied under local anesthesia. A diagnosis of "lymphoma of the parotid gland falling into the group of Mikulicz disease" was made with some reservations by the pathologist. X-ray therapy was given (1800 r to left gland and 1139 r to right gland). The parotid swellings receded and have not recurred. During the intervening years she has developed xerostomia and keratoconjunctivitis sicca as well as a pancytopenia. On re-evaluation the biopsy revealed the typical pathological picture of the parotid in Sjogren's disease.

CASE 9. H.S. No. 679363. This 47 year old white female complained of episodes of bilateral parotid swelling for several years. Swelling was often accompanied by pain. One month prior to being seen she had developed bilateral parotid swelling accompanied by pain and fever up to 104° F. The swelling subsided considerably under antibiotic therapy only to have the left side recur one week after therapy was stopped. The left parotid was diffusely enlarged and tender while the right gland was slightly enlarged. Pus could be expressed from Stensen's duct on the left. Culture was reported as showing Escherichia Coli, Micrococcus species and Alpha Streptococci. The mouth and pharynx were dry. An ophthalmologist diagnosed keratoconjunctivitis sicca. A left subtotal parotidectomy was performed under general anesthesia on May 9, 1957. The facial nerve was not injured. Histology was typical for Sjogren's Syndrome. This was a case of Sjogren's Syndrome with a secondary bacterial parotitis of such severity that a subtotal resection was indicated to control symptoms. Since operation two years ago she has had one mild episode of swelling on the other side which was easily controlled medically. As one would expect, there was no increase in xerostomia after the operation as parotid function had been completely destroyed by the disease.

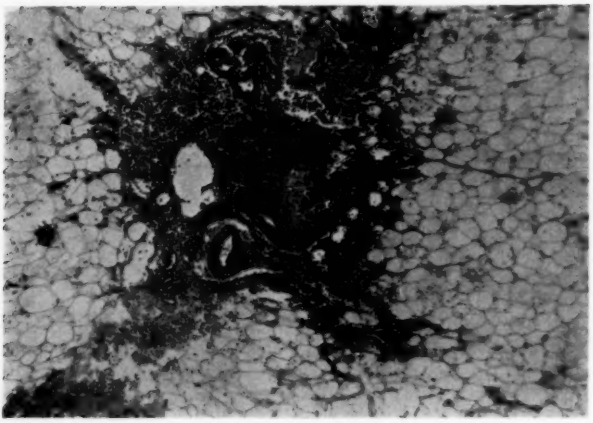

Fig. 6.—Case ten. Far advanced Sjogren's syndrome. The acini have disappeared and are replaced by fat cells. Small foci of lymphoid infiltrations are seen.

CASE 10. S.R. No. 681690. This 39 year old white female complained of recurrent episodes of unilateral and bilateral parotid swelling for over 15 years. Swelling would last about one week. She had had no enlargement for two years when seen on July 1, 1957. No saliva or pus could be expressed from Stensen's ducts. No parotid swelling was noted. She had severe xerostomia and had arthritis of the rheumatoid type. An ophthalmologist reported classical keratoconjunctivitis sicca. Left parotid biopsy was done under local anesthesia (Fig. 6). The acini were completely absent and replaced by fat cells. There were small areas of dense lymphoid infiltration surrounding small ducts and blood vessels. No epithelial islands were seen. Clinically this is a typical case of far advanced Sjogren's syndrome. The pathological findings are similar to those described in autopsy material. The acini have disappeared and are replaced by fat. The typical inflammatory changes seen in the other cases are absent. This may be the end stage of the inflammatory lesion or a case of Sjogren's syndrome showing only primary atrophy uncomplicated by secondary inflammation.

COMMENT

Some of the literature on Mikulicz disease and Sjogren's syndrome has been reviewed. A brief clinical summary of ten cases has been presented. Four cases were considered to have Mikulicz disease (three on pathological grounds and one on clinical features only) and six cases of Sjogren's syndrome were described. Five of the Sjogren's cases showed the same pathology in the parotid as did the three cases of Mikulicz disease in which tissue are available.

Morgan[4] has given us an excellent description of pathological findings common to the two conditions. Others have described the findings in the parotid in Sjogren's syndrome to be somewhat different than in Mikulicz disease. We have 8 cases which show the pathology described by Morgan and Morgan and Casteman.[3] In one late case of Sjogren's syndrome findings were similar to those described mainly in postmortem examinations.[17]

The definitive lesion consists of a progressive hyperplasia of the epithelial and myoepithelial cells of the intralobular ducts. At the same time the ducts are surrounded by a diffuse infiltration of lymphoid cells and the surrounding acini disappear. The ducts become solid cords which on section look like islands (epimyo-epithelial island or epithelial islands). Hyaline degeneration of the islands may take place. The lesion begins in foci which enlarge and coalesce. The lobular pattern of the gland is retained. The essential pathological phenomenon of this condition is the formation of the epithelial islands which do not occur in any other parotid disease except Mikulicz disease and Sjogren's syndrome. The fibrosis described by Morgan and Raven[14] has not been a prominent finding in our material. Epithelial islands were prominent in our two cases of localized Mikulicz disease which does not agree with Bernier and Bhaskar[10] who report that they are absent or only rarely seen in the localized form. Most other authors reviewed also find similar pathology in both groups. There is no evidence from our material that this is primarily a lymph node disease as concluded by Freund and Jonassen[6] and also by Bernier and Bhaskar.[10] Early lesions (Cases 4, 5, and 6) seem to indicate the lesion is primarily one of the intralobular ducts and surrounding acini. In Sjogren's disease the lesion is always bilateral and diffuse whereas in Mikulicz disease it is usually unilateral and may be either diffuse or localized.

Although Foote and Frazell[22] feel this lesion may be benign neoplasm the clinical behavior and pathological findings indicate to most workers that it is a chronic inflammation. The etiology remains obscure. It does not appear to be a bacterial infection although a secondary bacterial infection can occur (Case 9). Virus studies have not yet been fruitful but further search for a virus would seem to be indicated.

In our opinion there has been no satisfactory name for this type of parotid inflammation. Du Plessis' suggestion of idiopathic chronic parotitis has merit but there are other types of parotid infection of equally obscure etiology in which pathological findings are quite different. Chronic parotitis as suggested by Patey and Thakray does not exclude these other types of inflammation. Benign lymphoepithelial lesion was advanced by Godwin as a name for this condition. However, subsequent workers have included many unrelated diseases including neoplasms under this heading and the term as now applied leads to much confusion and probably should not be used. Mikulicz disease has historical significance but otherwise is not satisfactory. Maxwell[11] recently suggested the term chronic lymphoepithelial sialadenitis which appears to be most appropriate.

It is evident that we are dealing with a pathological process in the parotid gland which can occur in two different clinical situations. One is a local disease of the gland which may occur in both males and females and the other is associated with systemic disease which almost always is seen in females. There does not seem to be any real evidence that Mikulicz disease is a less highly developed form of Sjogren's disease as suggested by Morgan.[4] A more acceptable theory has been put forth by Du Plessis. He feels that the primary atrophy of the parotid acini in Sjogren's disease results in diminished flow of saliva which makes the gland peculiarly susceptible to a form of parotitis which occurs only rarely without the primary atrophy.

Sialography has been utilized in the diagnosis of salivary gland disease since 1925.[23] Many authors have described the finding of sialectasis or sialangiectasis as Swinburne[24] prefers to call it. Peripheral pooling of contrast media is variously called small duct, terminal or glandular sialectasis whereas a generalized dilatation of the large ducts due to an obstructive lesion may be called large duct sialectasis. Terminal sialectasis has been described as a congenital condition[25] but is

commonly reported as being found in chronic inflammatory lesions. Although it has been reported in chronic bacterial parotitis some authors believe it to be specific for the parotitis seen in Mikulicz disease and Sjogren's syndrome. The peripheral pooling of the contrast medium is generally considered to be due to dilation of the terminal parotid ducts.[26] Thakray[27] in an excellent study of parotid glands which had been surgically resected from patients showing sialectasis report that the sialectatic picture is mainly due to a rupture of ducts weakened by disease with subsequent extravasation of the contrast material into the periductal tissues. Our small amount of material does not shed any further light on the mechanism responsible for the sialectatic roentgenograms. Only occasionally a dilated duct is seen (Fig. 4) and we have not observed any spaces in the interstitial tissue which could be interpreted as recently or remotely extravasated contrast material. Further studies similar to those of Patey and Thakray[4] and Thakray[28] are necessary. In any case a finding of sialectasis on a sialogram is an important adjunct to diagnosis but should be supplemented by histopathological examination if possible.

As localized parotid lesions cannot be diagnosed accurately by clinical methods they should all be removed by a subtota parotidectomy. Occasionally a case of Mikulicz disease will be discovered. Recurrence may be treated by further surgery or x-ray therapy. While a presumptive diagnosis can be made on the diffuse form of Mikulicz disease by a sialogram which shows sialectasis a parotid biopsy should be done to make a definite diagnosis. A biopsy of the parotid gland is a simple innocuous procedure.[28] Symptoms are often mild and no treatment may be necessary once the diagnosis is established. Often the swelling subsides spontaneously. Surgery or x-ray therapy may be indicated if symptoms warrant.

The management of Sjogren's disease is usually supervised by the specialist in internal medicine with advice from consultants in ophthalmology and otolaryngology. Treatment is mainly symptomatic. The disease is slowly progressive. All suspected cases should have a sialogram and a parotid biopsy, whether or not the gland is enlarged, both for diagnostic purposes and to obtain more pathological information. Occasionally (Case 9) secondary bacterial inflammation became so severe as to require conservative parotidectomy. X-ray therapy is contra-indicated as it would tend to destroy any remaining functional salivary tissue in the oral cavity and pharynx.

Diamant[29] recommends ligation of the parotid duct for recurrent parotitis. However, no pathological information is given as to the type of lesion treated. If this minor procedure is applicable for the type of pathology described in this report it would seem to be the treatment of choice.

SUMMARY

1. Some of the literature on Mikulicz disease and Sjogren's syndrome as they involve the parotid gland has been reviewed.

2. Four cases of Mikulicz disease and six cases of Sjogren's syndrome have been presented.

3. The lesion appears to be a hyperplasia of the epithelial and myo-epithelial cells of the intralobular ducts which become solid cords and appear as islands on section. Concomitantly there is a periductal lymphoid infiltration and disappearance of acini.

When this lesion occurs in the salivary glands (usually in the parotid) without evidence of system disease it is called Mikulicz disease, benign lymphoepithelial lesion and many other names. The term chronic lymphoepithelial sialadenitis would seem preferable. The same pathological picture is usually seen accompanying a systemic disease called Sjogren's syndrome.

4. Most workers agree this is a chronic inflammatory lesion of unknown etiology which runs a benign course. Secondary bacterial infection may supervene causing more severe clinical symptoms.

5. A picture of sialectasis on a sialogram is suggestive of this pathological lesion. Whether the sialectasis is due mainly to dilated terminal ducts or to extravasated contrast medium is not yet clear.

6. Diagnosis and management are briefly outlined.

950 East 59th St.

REFERENCES

1. Schaffer, A. J., and Jacobsen, A. W.: Mikulicz Syndrome; Report of 10 Cases. Am. J. Dis. Child. 34:327-346 (Sept.) 1927.

2. Godwin, John T.: Benign Lymphoepithelial Lesion of the Parotid Gland. Cancer 5:1089 (Nov.) 1952.

3. Morgan, W. S., and Castleman, B.: Mikulicz Disease—A Clinico-Pathologic Study. Am. J. Path. 29:471 (May-June) 1953.

4. Morgan, W. S.: Mikulicz Disease—Probable Systemic Nature—Relation to Sjogren's Syndrome. New England J. Med. 251:5 (July 1) 1954.

5. Patey, D. H., and Thakray, A. C.: Chronic "Sialectatic" Parotitis in Light of Pathological Studies on Parotidectomy Material. Brit. J. Surg. 43:43-50 (July) 1955.

6. Freund, H. R., and Jonassen, O.: Benign Lymphoepithelial Disease of the Parotid Gland. Ann. Surg. 142:895 (Nov.) 1955.

7. Kay, S.: Mikulica Disease of the Salivary Glands. Am. J. Clin. Path. 26:291 (March) 1956.

8. Orloff, M. J.: Benign Epitheliolymphoid Lesions of the Parotid Gland. Papillary Cystadenoma Lymphomatosum and Mikulicz Disease. Internat. Abstr. Surg. 103:521 (Dec.) 1956.

9. DuPlessis, D. I.: The Problem of Mikulicz Disease. South African M. J. 32:264 (Mar.) 1958.

10. Bernier, J. L., and Bhaskar, S. N.: Lymphoepithelial Lesions of the Salivary Glands. Cancer 11:1156 (Nov.-Dec.) 1958.

11. Maxwell, James H.: Chronic Lympho-epithelial Sialadenopathy. Wherry Memorial Lecture. Tr. Am. Acad. Ophth. (Oct. 14) 1959.

12. Gougerot, H.: Bull. Med. 40:360, 1926.

13. Houwer, A. W. M.: Diseases of Cornea. Keratitis Filimentos and Chronic Arthritis. Tr. Ophth. Soc. U. Kingdom 47:88, 1927.

14. Sjögren, H.: Zür Kentnis der Keratoto-conjunctivitis sicca. Acta Ophth. Supp. No. 2 1-151, 1933.

15. Morgan, A. D., and Raven, R. W.: Sjogren's Syndrome: A General Disease. Brit. J. Surg. 40:154 (Sept.) 1952.

16. Gurling, K. J.: Association of Sjogren's and Felty's Syndromes. Ann. Rheumat. Dis. 12 (Sept.) 1953.

17. Cordell, B. S., and Gurling, K. J.: Observations on the Pathology of Sjogren's Syndrome. J. Path. and Bact. 68:137 (July) 1954.

18. MacLean, K., and Robinson, H. S.: Sjogren's Syndrome. Canad. M. A. J. 71:597 (Dec.) 1954.

19. Coverdale, H.: Sjogren's Syndrome as a Constitutional Defect. New Zealand M. J. 54:641 (Dec.) 1955.

20. McLenachan, J.: New Aspects of the Etiology of Sjogren's Syndrome. Tr. Ophth. Soc. U. Kingdom 76:413, 1956.

21. Heaton, J. M.: Sjögren's Syndrome and Systemic Lupus Erythematosus. Brit. M. J. 1:466 (Feb. 21) 1959.

22. Foote, F. W., and Frazell, E. G.: Tumors of the Salivary Glands. Cancer 6:1065 (Nov.) 1953.

23. Rose, S. S.: A Clinical and Radiological Survey of 192 Cases of Recurrent Swellings of the Salivary Glands. Ann. Roy. Coll. Surgeons England 15:374 (Dec.) 1954.

24. Swinburne, G.: Sialoangiectasis. Brit. J. Surg. 27:713-716 (Apr.) 1940.

25. Pearson, R. S. B.: Recurrent Swelling of Parotid Glands. Arch. Dis. Childhood 10:363-376, 1935.

26. Rubin, P., and Besse, B. E.: The Sialographic Differentiation of Mikulicz Disease and Mikulicz Syndrome. Radiology 68:477 (Apr.) 1957.

27. Thakray, A. C.: Sialectatis. Arch. Middlesex Hosp. 5:151, 1955.

28. Hemenway, W. G., and Allen, G. W.: Chronic Enlargement of the Parotid Gland: Hypertrophy and Fatty Infiltration. Laryngoscope 69:1508 (Dec.) 1959.

29. Diamant, H.: Ligation of the Parotid Duct in Chronic Recurrent Parotitis. Acta Oto-laryng. 49:375 (Sept.-Oct.) 1958.

LXIII

ARYTENOIDECTOMY IN CHILDREN

ROBERT E. PRIEST, M.D.

HAROLD S. ULVESTAD, M.D.

FRANK VAN DE WATER, M.D.

ROBERT J. RICHARDSON, M.D.
(by invitation)

MINNEAPOLIS, MINN.

This paper presents three cases of bilateral abductor paralysis of the vocal cords treated first by tracheotomy and later by arytenoidectomy. Such cases are commonplace and normally would not justify a special report; but our three patients were children, and arytenoidectomy is usually not done in children. We hope that this report may prove to be worthwhile as a means of directing attention to the occasional pediatric situation in which arytenoidectomy will be useful. The fact that in our own community we found three cases of arytenoidectomy in children suggests that the condition may not be rare, and that many unreported cases exist. It is true that references to arytenoidectomy in children are hard to find in the literature. Two of our cases had their paralyses as a result of poliomyelitis and in one the cause was never determined. In all three cases arytenoidectomy resulted in relief of stridor and permitted comfortable breathing without the use of a tracheotomy cannula. A brief summary of the literature with reference to vocal cord paralyses in children and arytenoidectomy follows.

The volume of written material describing vocal cord palsies in children is not great. In an excellent paper published by Florence Cavanaugh[1] of Manchester, England, in 1955, a comprehensive discussion is given. Cavanaugh reviews the literature from 1882 to 1955, and quotes some authors carrying the review back as far as 1872.

From the Division of Otolaryngology, University of Minnesota Medical School, Minneapolis, Minnesota.

Most authors report one or two cases of unilateral or bilateral vocal cord paralysis in children of various ages. In literature reviewed by Cavanaugh, and pertaining only to children, causes of the paralyses are legion. Causes include typhoid, diphtheria, syphilis, tuberculosis; adherence of the thymus to the pericardium and all structures of the neck including the recurrent nerve; epidural and subdural hematomata; 32 cases from the Philippines in children suffering from beri-beri; meningocele and hydrocephalus; toxic reaction from antimalarial drugs, and tumor of the fourth ventricle with extension into the pons. Numerous cases in which the cause of the bilateral paralysis was undetermined also appear.

Cavanaugh reports her own experience with 107 children having laryngeal lesions of various types, of which 37 were vocal cord palsies. She gives detailed information as to the duration of the paralyses and many other points. This material will not be recapitulated here, but is well presented in her paper for anyone who has a particular interest in this problem.

Inasmuch as we are dealing with bilateral abductor vocal cord paralysis here, it is of interest that of the four children seen by Cavanaugh with complete bilateral abductor paralysis, three showed no change, one after 4½ years, one after 6 years, and the third died after 3 months. The fourth child could not be persuaded to attend the clinic and be evaluated.

Quoting further from the same author's paper: "In most of the published series of vocal paralysis in adults, a large number of cases have been of unknown etiology and this investigation has been similarly disappointing." In her own cases, Cavanaugh was able to establish the following causes for paralyses, some permanent and some temporary: Measles at age 2½ years; pneumonia at age 3 months; tuberculosis of the right pulmonary apex; cystic hydroma with possible damage to the vagi at operation to remove the tumor; Arnold-Chiari malformation with associated meningocele.

Turning to other authors we find that Heatley[2] and Work[3] each described children with laryngeal paralysis and meningocele. In the Arnold-Chiari malformation, a tongue of cerebellar tissue in the midline herniates through the foramen magnum and descends over the posterior aspect of the cord, sometimes as low as the sixth cervical

segment. Associated with this, one finds elongation of the medulla. The foramen magnum may be occupied by the medulla as well as the tongue of cerebellum. Pressure is exerted on the medulla or the nerves emerging from it.

The only mention of an operation to restore the laryngeal airway by fixing one of the vocal cords in abduction found in our review of the literature pertaining to children is that of Cavanaugh. She said: "I had expected that this boy would need an operation to fix one of his cords in abduction—but he has learned the knack of breathing at just the right depth. He even plays games, but if his controlled breathing gets out of hand, he just moves to the side of the field and sits down until he is under control again!" The author then describes one occasion in which the boy enjoyed a game so much that he produced laryngeal syncope by overtaxing himself. This is the only occasion on which he overtaxed himself, she says. Therefore she did not feel justified in persuading the parents to consent to an operation.

A few other instances of laryngeal paralysis in children were located in the literature. Clerf[4] reported a boy of 14 years with bilateral recurrent laryngeal nerve paralysis following measles. Ross and Chambers[5] describe a unilateral paralysis in a child 11 months old in which the diagnosis of a lesion of the pons with pressure on the vagus nerve was suggested clinically and corroborated by autopsy.

The paper of Ross and Chambers presents an excellent differential diagnosis of recurrent nerve paralysis, together with good illustrations of the nerves and their relationship as they branch from the vagi and course upward to the larynx.

The main disability caused by bilateral abductor paralysis of the larynx is reduction of the size of the airway on inspiration. The vocal cords are always adducted, and are sucked together further on inspiration. This causes dyspnea and marked stridor. Surgical procedures are directed at restoring the airway. Tracheotomy bypasses the obstruction. Valved tracheotomy tubes permit expiration through the larynx with normal speech. Various plastic procedures on the larynx restore the laryngeal airway but usually compromise the voice somewhat. The usual cause for bilateral abductor paralysis is injury to the recurrent laryngeal nerves during thyroidectomy. The motivation for the development of the plastic corrective measures referred

to above has been the desire to rehabilitate postthyroidectomy cases, for the most part. In this paper the application of one of these techniques to patients having paralysis not due to surgical trauma is discussed.

The original laryngeal plastic surgical treatment of bilateral recurrent laryngeal nerve paralysis with fixation of the cords in a midline position, with resultant stridor was reported by King.[6] King transposed the omohyoid muscle and attempted to have it produce abduction of the arytenoid cartilage. This proved to be unsatisfactory.

In 1941, Kelly[7] resected the arytenoid through a window made in the ala of the thyroid cartilage. Orton[8] advised removal of the posterior portion of the wing of the thyroid cartilage to facilitate approach to the arytenoid cartilage. Woodman[9] recommended partial arytenoidectomy with retention of the vocal process and fixation of the vocal cord to the inferior cornu of the thyroid cartilage. Thornell[10] later reported transpharyngeal removal of the arytenoid cartilage for bilateral abductor paralysis together with his results in three cases. Since then other reports such as the one by Havens[11] have indicated that this procedure is satisfactory.

The standard procedures carried out now for the relief of bilateral recurrent laryngeal nerve paralysis with midline fixation of the cords involve arytenoidectomy, either intralaryngeal by the method of Thornell, or extralaryngeal by techniques advocated by Kelly, Woodman, King, and others. One or both arytenoids may be removed. The end result is abduction of the posterior end of the operated cord while the anterior end of the cord stays in adduction and permits production of an audible voice. If the airway created by the arytenoidectomy is adequate, the patient can be relieved of his tracheotomy cannula and the opening into the trachea can be closed. Of course, the alternative to these procedures is either continuing dyspnea and stridor or the wearing of a valved tracheotomy cannula permitting inspiration through the tracheotomy and expiration through the larynx when the valve closes.*

Reports of three cases treated by the authors or their associates follow. All patients were children having bilateral abductor paralysis

* Note supplementary references at the end of the paper.

of the larynx relieved by arytenoidectomy. Two of the children had paralysis due to polio, and in one the cause was never determined despite extremely vigorous and extensive study. In all cases relief of stridor and dyspnea occurred and decannulation was carried out. Social rehabilitation was successful and the children all are attending school without wearing tracheotomy tubes. A colored talking motion picture of the three children was presented at the conclusion of the paper so that breathing, general attitudes, and clinical results could be assessed by the listening audience.

REPORT OF CASES

CASE 1. J.S., University of Minnesota Hospital No. 806000, male, born June 29, 1945. (Operated upon by Dr. L. R. Boies, University Hospital, Minneapolis, Minnesota.) This boy suffered acute bulbar poliomyelitis in June and July of 1949 with paralysis of the abducens, facial and hypoglossal nerves; he had an inspiratory and expiratory stridor. Tracheotomy was done on June 22, 1949, and when decannulation was decided upon, the tube could not be removed because of dyspnea. Direct laryngoscopy on July 20, 1949 revealed bilateral vocal cord paralysis; the cords were fixed in the midline; they could not be abducted.

The boy was readmitted to the hospital in October of 1949 for re-evaluation of his laryngeal innervation and vocal cord paralysis. The midline paralysis was still present, and decannulation was not carried out. The left abducens and hypoglossal nerves remained paralyzed. Re-evaluation in July of 1950 showed some movement of the right cord and none in the left, and decannulation was carried out successfully. The patient was readmitted to the University Hospital with a diagnosis of bronchopneumonia in 1951. The patient continued to have persistent laryngeal stridor, although tracheotomy was not needed after decannulation. Because there was so much stridor and so much difficulty with respiration, and because the boy's glottis was narrowed, he was admitted to the hospital in August 1951, and arytenoidectomy was carried out. The right arytenoid was approached through an external incision and removed by a modification of Woodman's operation. The patient was relieved of his stridor and was able to breathe without his tracheotomy tube after the operation. The tube was left in for 10 days after the surgery. The patient still has

some inspiratory stridor but has a good voice and has been normally active to the present time without complications.

CASE 2. J.S., age 16, male (operated upon by Dr. Harold S. Ulvestad at Methodist Hospital, Minneapolis, Minnesota). This boy suffered bulbar poliomyelitis in 1952 at the age of nine years. Treatment at the Sister Kenny Institute in Minneapolis included a tracheotomy. Decannulation was accomplished by the time the boy was discharged from the hospital, although the airway was definitely and persistently diminished. For the next four years, he was able to go to school, but his physical activity was restricted and his weight remained constantly at 60 pounds.

In June of 1956, he developed an acute upper respiratory infection and laryngitis requiring an emergency tracheotomy by his family doctor. Three weeks later, he was first examined by Dr. Ulvestad. There was almost complete paralysis of both vocal cords in the paramedian position. The larynx appeared to be much smaller than normal for a boy his age. No treatment was prescribed other than the continued wearing of the tracheal tube. After two months had passed, the boy's weight had increased by 9 pounds, and he was generally stronger and more active. General improvement continued, although the boy did not tolerate the closing off of the tracheostomy.

In August 1957, 14 months after his first examination by Dr. Ulvestad, he was admitted to the hospital, and a Woodman type arytenoidectomy was performed on the right vocal cord. The arytenoid was removed and the posterior end of the right cord was sutured into a position of abduction. The tracheal cannula was removed one month later. Breathing was improved, although the voice was not as good as before surgery. The boy was able to return to school and ordinary activity with only moderate restriction. Two years later, he was again admitted to the hospital for closure of the persistent 1 mm sized tracheostomy stoma. His postoperative course following this surgery was uneventful. On the day of discharge from the hospital, he was able to climb 4 flights of stairs rapidly and without difficulty. Closure of his tracheal stoma apparently had no significant effect on his respiration. His general condition has remained good.

CASE 3. K.T., female, born May 23, 1952. (Operated upon by Dr. Robert E. Priest, at St. Mary's Hospital, Minneapolis, Minnesota,

referred by Dr. John P. Kelly, Minneapolis). At about the age of 8 months, on February 18, 1953, direct laryngoscopy was carried out at St. Mary's Hospital, Minneapolis, because of stridor which may have appeared first at the age of 3 months. The stridor was worse on inspiration, and there was some indrawing of the pretracheal tissues during inspiration. The larynx was examined with a Tucker twin lighted laryngoscope, and the vocal cords were not seen to abduct during inspiration. The opening which did form between them was fusiform in shape. The opening formed a long narrow ellipse and there was no more opening at the posterior end than at the anterior end. The anterior two-thirds of the cords were sucked down into the laryngeal aperture and this mechanism produced the noise. A 4 mm bronchoscope was passed into the trachea and the trachea and main bronchi were found to be normal. As the bronchoscope was withdrawn, it was seen that the arytenoids were pushed wide apart. This showed that there was no anomaly or ankylosis of the cricoarytenoid joint. On the other hand, there was no positive abduction of the cords. The attempt to discover the cause for this child's bilateral abductor paralysis included an esophagogram which showed no evidence of vascular ring; a chest film was normal except for bilateral basilar bronchitis and questionable pneumonitis. General examination was extensive and did not explain the cord paralysis.

On June 11, 1953, when the child was a little bit older than one year, the larynx was again visualized and conditions were identical to those seen on the first laryngoscopy. An airway was established by passing an endotracheal tube through the larynx, and a tracheotomy was carried out through the third or fourth tracheal ring. The child got along nicely with the increased airway, and definitely could not tolerate occlusion of the airway.

On January 19, 1954, the patient was referred to Dr. Paul Adams at the University of Minnesota Heart Hospital for cardiac evaluation. In his summary of the case, Dr. Adams noted that the patient had apparently been normal until approximately 3 months of age, at which time she developed laryngeal stridor which became progressively more severe. After her tracheotomy, her disposition, appetite and weight gain had been satisfactory. He noted that a heart murmur had been heard at St. Mary's Hospital prior to the reference of the patient to him at the University Hospital, and that configuration of the heart on x-ray at St. Mary's Hospital was slightly abnormal. This

abnormality had consisted of a slight and somewhat questionable right heart border.

On physical examination by Dr. Adams, the blood pressure was 88/50 mm mercury. The child was not cyanotic, was alert and healthy. No retraction or stridor were seen. The chest was normal, the heart tone and rate were normal, but there was a hollow-sounding soft systolic murmur in the pulmonic area. The femoral arteries were palpable.

The electrocardiogram showed a tendency to left axis deviation. There was a W configuration of the QRS complex in lead 3, and rr' in V1 suggesting a left ventricular hypertrophy.

The six foot heart films and cardiac fluoroscopy revealed a slightly enlarged heart. There was a slight congestion of the bronchial and vascular markings suggesting a left to right shunt. The pulmonary artery segment and the left atrium were increased, but these abnormalities seems to be less noticeable on the films made at the University Hospital than on the films made previously at St. Mary's Hospital. There was a shadow in the right upper mediastinum compatible with thymic enlargement, or perhaps right azygos lobe atelectasis.

It was Dr. Adams' impression that there probably existed an underlying congenital defect of undetermined origin. This could be an atypical patent ductus arteriosus. However, Dr. Adams did not feel that there were any primary cardiac symptoms unless the laryngeal paralysis was related to the patent ductus.

In his opinion, this could account for a left recurrent laryngeal nerve paralysis, but could have nothing to do with the right laryngeal nerve paralysis. It was Dr. Adams' opinion that further investigation of the cardiac status could be deferred until a later age, at which time the underlying pathology in the chest would be more evident, and cardiac studies would involve less risk and perhaps be more satisfactory. For this reason, the child was carried with tracheotomy from that point on, and no further attempt was made to elucidate the cause of the vocal cord paralysis for the time being.

In June 1955, at St. Mary's Hospital, the larynx was again exposed with an infant laryngostat, and the cords were seen to be fixed

in the midline. They were pushed out of the way using a 4 mm bronchoscope, and were found to be freely movable. This was exactly the same condition previously found on laryngoscopy. The child was equipped with a No. 3 tracheotomy tube instead of the previously worn No. 2 tube.

In February 1956, in order to permit the child to talk without closing her laryngeal tube, a No. 3 Tucker valved tracheotomy tube was prepared by the Pilling Company in Philadelphia. The child would not accept this tube, and her use of it was completely unsatisfactory, and we could never give her the benefit of speech without the necessity of closing her tracheotomy stoma.

In the spring of 1957, this little girl was facing the prospect of entering school at the age of 5 years. It was extremely desirable that she be relieved of her tracheotomy cannula. After much consideration and repetition of most of her studies, it was determined that the possibility of finding a cause for her laryngeal nerve paralysis through further cardiac studies was not great. Therefore, arytenoidectomy was decided upon as the best means for supplying her with a laryngeal airway large enough to permit her to discard her tracheal tube, and close her tracheal stoma. On June 24, 1957, the right arytenoid was removed by the operation of Woodman. Our intention was to leave the vocal process of the arytenoid in place, but it was so short in this young child that it was completely dissected out before the operator realized that he had reached the anterior end of it. An attempt to put a bridle suture through the mucous membrane of the cord and pull the cord laterally resulted in opening through the mucosa into the larynx, exposing the endotracheal anesthesia tube. Therefore, it was decided that suturing the cord laterally could not be done, and closure of the tissues over the arytenoid area was made in layers. Because the vocal process of the arytenoid was not left in place, and the cord was not sutured laterally, this was not truly a Woodman operation, but probably was as close an approximation of it as could be carried out in so young a child.

In June 1957, the patient was discharged from the hospital with the neck wound healed. She could close her tracheotomy tube quite nicely and breathe without difficulty. She had a small amount of leakage of liquid into the trachea when she swallowed. By July 17, 1957, the size of the tracheotomy cannula was reduced from No. 3

to No. 1, and the little girl could not detect the difference between the various tubes. In late August, the tube was removed entirely, and by August 26, the fistula had closed to about half of its original size. The child was doing well but was very apprehensive at the lack of a tracheotomy tube. Of course, she had worn a tube since her earliest memory, and her fright at having it out of her neck was quite marked. For this reason, the tracheal stoma was not closed surgically until January 1958. Then the skin around the stoma was dissected out, and the stoma was closed in layers.

The patient got along quite well but with some dyspnea and with some stridor. She entered school on schedule in September 1957, without a tracheotomy tube in place. She has been admitted to the hospital with respiratory infections on several occasions since decannulation. She always has marked stridor with these infections. She is a source of considerable worry to the house staff of the hospital when she comes in when they do not know her previous history. Her stridor always seems extremely marked. On one occasion, she was narrowly saved from the introduction of an endotracheal tube by an overzealous resident who came upon her in the middle of the night when she was making considerable noise during a respiratory infection. Without troubling himself to find out about her previous history, he obtained a laryngoscope and an endotracheal tube, and set out to intubate her. Fortunately someone familiar with her history appeared on the scene in time or we might have had to reinsert our tracheotomy cannula, after such a painful and long effort to remove it.

In December 1957, the parents and physician became concerned over the child's lack of growth. She was studied carefully by Dr. Rolf Andreassen who is a cardiologist in Minneapolis. It was his conclusion that "we have no evidence of heart disease or any vascular ring around the trachea and esophagus to account for her bilateral paralysis of the recurrent laryngeal nerves. There is definite retardation of maturation and growth in the skeleton, cause of which is not clear." Dr. Andreassen went on to say that he believed that thorough study of the child's endocrine system should be made in an attempt to discover the reason for retardation of bone growth.

For the purpose of this study, the child was referred to Dr. John Anderson, Professor of Pediatrics at the University of Minnesota Medical School. It was his conclusion that the child was not a dwarf,

as had been feared, but that she fitted into the lower end of the normal growth curve for children of her age. He felt that her retarded epiphyseal development also fitted properly into this level.

Since 1957, the little girl has done well except for the difficulty with acute respiratory infections detailed above. She is blessed with a higher than average intelligence and the personality of an extrovert despite her many trials. These attributes stand her in good stead in school. She loves to appear before the class and talk and is an excellent student. Her condition tends upward as she grows older. We feel that she probably has some anomaly within her chest, because she has developed some large veins on the right side of her neck, and to some degree upon her lower thorax. However, we feel that cardiac surgery certainly is not indicated since she is getting along this well, and it is likely that she will have a normal life despite her medical problems.

SUMMARY

This paper has presented three cases of bilateral abductor paralysis of the vocal cords treated first by tracheotomy and then by arytenoidectomy. These cases justify a special report only because they all occurred in children. Two were in patients suffering from bulbar poliomyelitis, and one was in a child having bilateral recurrent nerve paralysis of unknown cause. In all cases, the arytenoidectomy permitted the children to remove and to discard the tracheotomy tubes with closure of the tracheostomy. The authors feel that because they were able to find three cases of arytenoidectomy in children in their own community, the condition may not be rare. However, references to arytenoidectomy in children are difficult to find in the literature. A review of the literature for the last ten years is presented, and detailed case histories are given.

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REFERENCES

1. Cavanagh, Florence: Vocal Cord Palsies in Children. J. Laryngol. and Otol. 69:399-418 (June) 1955.

2. Heatley, C. A.: Arch. Otolaryng. 29:90-103, 1939.

3. Work, W. P.: Arch. Otolaryng. 34:267-280, 1941.

4. Clerf, Louis H.: The Surgical Treatment of Bilateral Posticus Paralysis of the Larynx. Laryngoscope 60:142-151 (Feb.) 1950.

Clerf, L. H.: Bilateral Abductor Paralysis of the Larynx; Results of Treatment by Modified King Operation. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 64:38-46 (Mar.) 1955.

5. Ross, D. E., Chambers, D. C.: Recurrent Laryngeal Nerve Paralysis Occurring in an Infant. Amer. J. Surg. 94:513-516 (Sept.) 1957.

6. King, B. T.: Progress in Dealing with Vocal Cord Paralysis. J. Internat. Coll. Surgeons 12:288-296 (May-June) 1949.

7. Kelly, J. D.: Surgical Treatment of Bilateral Paralysis of the Abductor Muscles. Arch. Otolaryngol. 33:293, 1941.

8. Orton, H. B.: Extralaryngeal Surgical Approach for Arytenoidectomy. Bilateral Abductor Paralysis of the Larynx. ANNALS OF OTOLOGY RHINOLOGY AND LARYNGOLOGY 53:303-307 (June) 1944.

9. Woodman, De G.: Bilateral Abductor Paralysis; Survey of 521 Cases of Arytenoidectomy via Open Approach as Reported by 90 Surgeons. A.M.A. Arch. Otolaryng. 58:150-153 (Aug.) 1953.

Woodman, De Graaf, and Pollack, Doreen: Bilateral Abductor Paralysis. Postoperative Care and Speech Therapy Following Arytenoidectomy. Laryngoscope 60:832-9 (Aug.) 1950.

Woodman, De G.: Rehabilitation of Larynx in Cases of Bilateral Abductor Paralysis; Open Approach to Arytenoidectomy with Report of Past Four Years' Experience. A.M.A. Arch. Otolaryng. 50:91-96 (July) 1949.

Woodman, De G.: Bilateral Abductor Paralysis; Arytenoidectomy for Bilateral Abductor Paralysis—Extralaryngeal Approach. Proc. Roy. Soc. Med. 45:821-826 (Dec.) 1952.

10. Thornell, W. C.: Intralaryngeal Arytenoidectomy in Bilateral Abductor Vocal Cord Paralysis. Surg. Gynec. and Obst. 95:63-66 (July) 1952.

Thornell, W. C.: Transoral Intralaryngeal Approach for Arytenoidectomy in Bilateral Vocal Cord Paralysis with Inadequate Airway. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 66:364-368 (June) 1957.

Thornell, W. C.: Intralaryngeal Approach for Arytenoidectomy in Bilateral Abductor Vocal Cord Paralysis. Tr. Am. Acad. Ophth. 53:631-636 (July-Aug.) 1949.

Thornell, W. C.: Intralaryngeal Approach for Arytenoidectomy in Bilateral Abductor Vocal Cord Paralysis. Tr. Am. Acad. Ophth. 53:631-636 (July-Aug.) 1949.

11. Havens, F. Z.: Bilateral Paralysis of Vocal Cords; Treatment by Transoral Arytenoidectomy. Laryngoscope 63:475-484 (June) 1953.

SUPPLEMENTARY REFERENCES

Lawson, H. P.: Treatment of Bilateral Abductor Vocal Cord Paralysis. J. Laryng. and Otol. 69:374-389 (June) 1955.

Carlens, E.: Bilateral Abductor Paralysis of Larynx. Acta Otolaryng. Supp. 116:57-62, 1954.

Morrison, L. F.: Evaluation of King Operation for Bilateral Abductor Paralysis of Laryngeal Muscles. Tr. Am. Goiter Ass'n. 247-261, 1954 (1953).

Grossman, A. A.: Modified Approach for Surgical Correction of Bilateral Abductor Vocal Cord Paralysis. Canad. M. A. J. 70:521-525 (May) 1954.

DeBord, B. A.: Paralytic Stenosis of Larynx: Modification of Intralaryngeal Approach to Arytenoidectomy. Laryngoscope 63:757-777 (Sept.) 1953.

DeBord, B.: Bilateral Abductor Paralysis of Larynx: Surgical Treatment. Texas J. Med. 48:635-636 (Sept.) 1952.

Hoover, W. B.: Surgical Procedures for Relief of Symptoms of Paralysis of Recurrent Laryngeal Nerves. Surg. Clin. N. America 33:879-885 (June) 1953.

Curkovic, M., and Horvatsky, M.: Extra-laryngeal Approach to Arytenoidectomy in Bilateral Paralysis of Abductors of Larynx. A.M.A. Arch. Otolaryng. 57:328-333 (Mar.) 1953.

Scheer, A. A.: Laryngofissure Approach in Surgical Treatment of Bilateral Abductor Paralysis. A.M.A. Arch. Otolaryng. 57:173-181 (Feb.) 1953.

Pearlman, S. J., and Killian, E. W.: Thyrotomy Approach for Arytenoidectomy in Bilateral Abductor Paralysis of Vocal Cords. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 62:207-212 (Mar.) 1953.

Edwards, T. M.: Progress in Surgical Treatment of Bilateral Laryngeal Paralysis. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 61:159-178 (Mar.) 1952.

Brown, L. A.: Intra-laryngeal Arytenoidectomy with Observations in Three Cases. Laryngoscope 61:332-340 (Apr.) 1951.

Von Leden, H.: Intralaryngeal Correction of Bilateral Abductor Paralysis; A Modification of Thornell Operation. Laryngoscope 60:1190-1200 (Dec.) 1950.

Faaborg-Anderson, K.: Recurrent Laryngeal Paralysis of Unknown Aetiology. Acta Oto-laryng. Supp. 118:68-75, 1954.

Ardran, G. M., Kemp, F. H., and Marland, P. M.: Laryngeal Palsy. Brit. J. Radiol. 27:201-209 (Apr.) 1954.

Capps, F. C. W.: "Abductor Paralysis" in Theory and Practice Since Semon. J. Laryng. and Otol. 72:1-31 (Jan.) 1958.

Barrett, J. H.: Surgical Treatment of Bilateral Abductor Paralysis. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 59:112-123 (Mar.) 1950.

Rethi, A.: Operation for Relief of Bilateral Vocal Cord Paralysis. J. Laryng. and Otol. 64:632-639 (Oct.) 1950.

Bosma, J. R., Goates, W. A., and Nielson, M. A.: Mechanisms of Disability of Speech Resulting from Poliomyelitis. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 66:67-85 (Mar.) 1957.

LXIV

EARLY INVASION OF THE THYROID GLAND IN CARCINOMA OF THE GLOTTIS

Ricardo Tapia Acuna, M.D.

México, D. F. México

In my experience, it is evident that a discrete lesion of one vocal cord, if there is no fixation at all, can be treated either by x-rays or by cordectomy. In cases not enough advanced to justify total laryngectomy, I follow the contralateral aperture of the larynx and always remove an anterior portion of cartilage. In just a few cases I included the removal of the corresponding alae of the thyroid cartilage. I have nothing to add to what has been said about ineffectiveness of x-ray therapy when there are lymph node metastases at the neck. I have nothing to add either to the indications for total laryngectomy as accepted today.

After Billroth's laryngectomy (1870), Gluck described a more or less perfect technique for treatment of carcinoma of the larynx. After him, many authors made some improvements with the definite purpose of giving a better exposure, avoiding the salivary fistula, making a better support of the neck and permitting a complete excision of the tumor.

In spite of all known improvements, a good diagnosis, as stated by C. L. Jackson, is the basis of the treatment. Nevertheless, according to the reports from everywhere, the failure of laryngectomy is frequent and it all depends on the invaded tissues left or on the presence of metastatic lymph nodes in the neck.

There is one thing that strongly attracted my attention and it is the appearance of growing of the thyroid cartilage in the presence of carcinoma, involving only the vocal cords and the anterior commissure. I have seen this without evidence of neck metastasis or invasion of the surroundings in four cases. In two of these cases I performed total laryngectomy in a simple way and there was a recur-

rence in both, within the first year; one locally and the other as a metastatic neck gland.

Apparently, only a few have given real importance to the possibility of invasion of the thyroid gland or its capsule, unless there are definite symptoms. I think we should give more importance to this fact. An example of it is the case I have the honor to present today in a motion picture. In this particular case, there was a microscopic invasion of the capsule of the right lobe of the thyroid gland in spite of absence of any other macroscopic sign. To me, the danger signal was the increase of size of the thyroid cartilage. From the embryological point of view, it is admissible that in some cases small portion of the thyroid gland remains inside the larynx, without giving symptoms for the rest of life. A few years ago, I saw a child 2½ years old who had suffered hoarseness since birth. At the date of examination, he was dyspneic and presented papillomas of the glottis. When resecting those tumors, one of them, at least, was found to be thyroid gland tissue. This child recovered after a few laryngoscopic removals of the tumors and they happened to be only papillomas, according to the pathologist. Never again was thyroid tissue seen in the specimens. Two years ago, I saw a female patient, 55 years old, with an obstruction of the glottic and subglottic spaces, on the left side. She had been quite well until three months before. I removed the tumor by open approach and found out that the cartilages were absolutely normal and the airway was independent from the thyroid gland. The report of the pathologist was: "thyroid gland tissue without evidence of tumoral development." So far, this patient is quite well and has not shown a recurrence. There is no doubt that in both cases it was nothing but endolaryngeal aberrant thyroid gland.

These two cases demonstrate once more the close relations between the intralaryngeal and extralaryngeal organs. The thyroid gland invasion is easily diagnosed in advanced cases, but it is rather difficult to do if the lesions are apparently limited to the glottis. The gland may be free of neoplasic cells, even if its capsule is microscopically invaded. Therefore, the removal of the larynx will not be enough to keep the patient free of the disease.

Recently, Louis and associates spoke about a paramedian incision as an important factor in total laryngectomy. I have found that it is

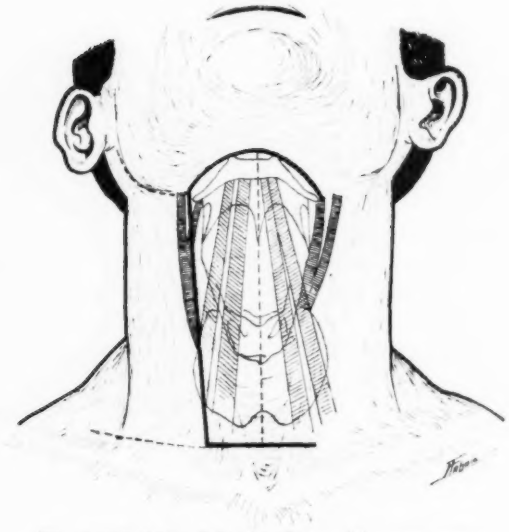

Fig. 1.—Incision of the skin for total laryngectomy.

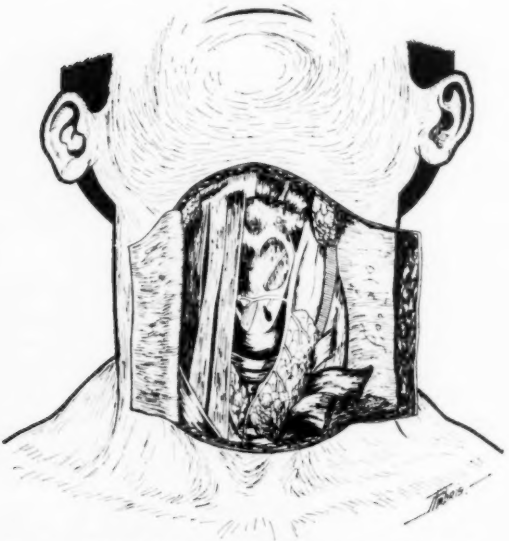

Fig. 2.—Wide field. Aponeurosis is cut at the middle line.

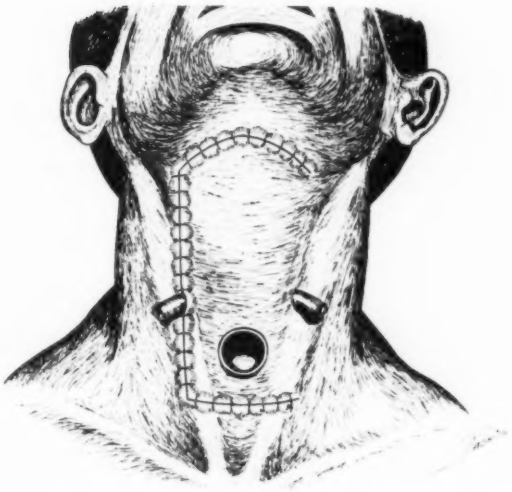

Fig. 3.—Total laryngectomy. Final aspect. Sub-aponeurotic drainage.

a real improvement in the technique. This incision is completed by two more: one transverse above and another below.

The skin flap is held to the opposite side and one can make a good inspection of both carotid regions and use the fingers to explore the presence of lymph nodes. Besides, in case it is found necessary to make a lateral dissection, the transverse incisions can be prolonged to either side in such a way that, without making extra cuts in the skin, it is easy to remove the whole contents.

Considering the different points of view, I am following a technique of total laryngectomy that in my opinion combines the advantages of those previously described: 1) a paramedian incision going from the right cornu of the hyoid bone to the suprasternal notch; an incision going from the upper end of the latter over the left side to the end of the left cornu of the hyoid bone following the upper margin of the last; another, horizontal incision, parallel to the last one, at the bottom; 2) dissection of the skin to bring a flap over the oppo-

Fig. 4.—Tomogram. Showing subglottic aberrant thyroid. Case No. 2.

site side of the neck; 3) opening of the aponeurosis in the middle line and prolongation of the incision up and down in both cases; 4) removal of the body of the hyoid bone; 5) if necessary, removal of the ribbon muscles; 6) skeletonization of the larynx from above downward, including ligature of the superior thyroid artery at the desired side; 7) partial or total dissection of the corresponding lobe to include it in the whole mass to be excised, if an enlargement of the thyroid cartilage is found; 8) opening of the trachea with a curved flap at the posterior wall; 9) removal of the larynx from below upwards including a large portion of the thyrohyoid membranes; 10) suture of the pharynx in two steps: the first one continuous and the second one interrupted (Cushing's), following a double line with upper angle; 11) placement of drainage with rubber tubes going from the skin, at each side of the middle line, to the subaponeurotic space; 12) suture of muscles and aponeurosis by interrupted cross lines with a No. 0 chromic catgut; just in case the ribbon muscles are preserved, there should be a double suture so that they are kept superposed; 13) fixation of the stoma through an opening in the skin; 14) suture of the skin at the level of the incision; 15) placement of the tracheal cannula and covering of the entire field with dry gauze. To have a better support of the neck, it is advisable to place an elastic bandage around it, but not too tight. The feeding tube is placed

Fig. 5.—Larynx specimen, right thyroid gland lobe included. Continuity of the tumor at the right side.

through the nose, before closing the pharynx. I prefer the Levine rubber tube, to avoid acid regurgitations from the stomach.

The postoperative care is more or less the same as usual. I usually remove the feeding tube after two weeks, not before.

Speaking with some qualified laryngologists I found that there is not a definite method of examination, on which we can depend, to

learn if the thyroid gland or its capsule is free of malignant invasion, unless the case is well advanced. If we pay more attention to the enlargement of the thyroid cartilage in spite of the presence of limited lesions at the glottis, and remove the corresponding thyroid lobe, we may think that we have done something more for the cure of the patient.

On the other hand, it is disappointing that some laryngologists advise neck dissection even without macroscopic lymph nodes and others think it is unnecessary. The mentioned incision makes it possible to perform laryngectomy after an open search and to complete the operation with a neck dissection, if indicated.

SUMMARY

A brief comment is made on the different procedures for treating carcinoma of the larynx.

A complete clinical, endoscopic and radiological examination guides the surgeon to make the right choice of treatment.

It is very difficult to diagnose invasion of the envelopment of the thyroid gland or the gland itself, unless the case is well advanced.

In spite of absence of other symptoms or signs, in the presence of enlargement of the thyroid cartilage it is advisable to remove partially such a gland, at the same time that a total laryngectomy is performed.

A paramedian skin incision, prolonged to the opposite side above and below, is adequate also for neck dissection, completed with another lateral flap, with only an elongation of both horizontal incisions on the desired side.

INSURGENTES S. 300

REFERENCES

1. Grossman, Arnold: The Treatment of Carcinoma of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 64:1067 (Dec.) 1955.

2. Leroux-Robert, Jean: Indications for Radical Surgery, Partial Surgery, Radio-Therapy and Combined Surgery and Radio-Therapy for Cancer of the Larynx

and Hypopharynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 65:137 (Mar.) 1956.

3. Lewis, G. Kenneth: Reconstruction Methods Following Laryngolpharyngectomy. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 66:86 (Mar.) 1957.

4. Norris, Charles M.: Technique of Extended Fronto-Lateral Partial Laryngectomy. Laryngoscope 65:1240 (July) 1958.

5. O'Keefe, John J.: The Surgery of Cancer of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 65:131 (Mar.) 1956.

6. Putney, F. Johnson: Preventive Dissection of the Neck in Cancer of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:136 (Mar.) 1958.

7. Sheline, Glenn E.: Carcinoma of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:1066 (Dec.) 1958.

8. Tapia Acuña, Ricardo: Glándula Tiroides Aberrante en Laringe. Gaceta Médica de México 88:899 (Dec.) 1958.

LXV

THE ROLE OF RADIATION THERAPY IN CARCINOMA OF THE LARYNX

JOSEPH L. GOLDMAN, M.D.

AND

SIDNEY M. SILVERSTONE, M.D.

NEW YORK, N. Y.

For the past three and one-half decades patients suffering from cancer of the larynx have been cured by radiation therapy in many clinics throughout the world.[1] While there have been swings of enthusiasm and pessimism for this form of therapy as it has developed, considerable experience and various impressions have been gained in this modality of treatment during this period of time. It seems that the recent interest in head and neck surgery has tended to push radiation therapy into the background. Unfortunately, many surgeons do not give radiation therapy the consideration it deserves in the treatment of laryngeal cancer. They are quick to point out the failures and complications of radiation therapy and to overlook the successes. It must be admitted that surgery, too, has its quota of risks, complications and failures.

It is our purpose to show that radiation therapy, as we know it today, has the potential to play an important, active role in the treatment of laryngeal cancer and should be regarded as an effective modality in its own right. Surgery and radiation therapy should not be considered as competitive therapeutic methods. While some lesions can be treated equally well by either modality, the results are not the same functionally. This does not deny that there are instances where one might succeed where the other would fail. We believe that the time has come when radiation therapy should be the preferential primary form of treatment for the small cordal carcinoma suitable for

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From the Departments of Otolaryngology and Radiotherapy, Mount Sinai Hospital.

partial laryngectomy. On the other hand, we recognize the fact that surgery is more effective as a primary method of treatment for laryngo-pharyngeal lesions, although results are poor with either modality. It is our opinion that the future successful handling of these cancers will depend more on a combination of radiation and surgery than on either form of therapy alone. Laryngeal cancer is in the unique position of having available two methods of treatment which have proved successful in a large percentage of cases, large, that is, for cancer. Cures might be increased if one modality is used to supplement the other.

We wish to state emphatically that success with radiation therapy requires expert management by those who are well trained and highly experienced in this field and who have the proper radiation facilities. Inexpert radiation therapy has no place in the treatment of laryngeal cancer and certainly is no substitute for surgery.

The authors have been involved actively in radiation therapy for laryngeal cancer for almost three decades—one (J.L.G.) since 1932 and the other (S.M.S.) since 1936. Together we have been studying this problem for 24 years, first as part of the group at The Mount Sinai Hospital originally started and headed by Dr. Rudolph Kramer and Dr. William Harris and then continued by ourselves and our staffs. Since 1931 patients treated by radiation for carcinoma of the larynx have been followed in a combined laryngeal-radiation therapy clinic which is held once every month.

Over this period of time, this group has studied 312 cases in which radiation was the primary form of treatment. While a number of radiation failures were cured subsequently by surgery, these cases were considered only as failures in our statistical analysis. Similarly, surgical failures which were cured by radiation also are not included in this study.

This series of cases is comprised of patients from the Otolaryngological Service and from the private practices of members of the staff of The Mount Sinai Hospital.

CLASSIFICATION

The literature on carcinoma of the larynx and laryngopharynx contains numerous and varied classifications. The lack of general

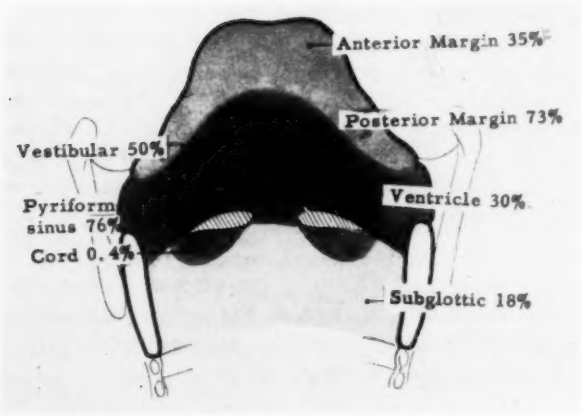

Fig. 1.—Percentage lymph node metastasis in 465 consecutive cases of carcinoma of larynx from Pietrantoni, L.: The Surgical Problem of Lymph Node Metastasis in Cancer of the Larynx.

agreement presents a serious and difficult problem in the comparison and evaluation of statistics and results. We are adhering to the classification presented by our original authors for the reason that it is based upon the practical aspect of prognosis.[2,3]

Our cases are divided into two major groups: the larynx proper or intrinsic larynx and the laryngopharynx or extrinsic larynx. The intrinsic larynx includes the vocal cords with the adjacent ventricular area above and subglottic area below and the anterior and posterior commissures. The laryngopharynx includes the false cords, epiglottis, aryepiglottic folds, arytenoids, pyriform sinuses and postcricoid region.

We have further subdivided our intrinsic laryngeal cases into those which could have been treated properly by partial laryngectomy and those which would have required laryngectomy. We are aware that there are some laryngologists who would perform hemi-laryngectomy in certain cases where others would prefer total laryngectomy.

TABLE I

CARCINOMA OF LARYNX AND LARYNGO-PHARYNX: 1931-1959
TREATED BY IRRADIATION

Total number of cases treated		312
INTRINSIC		179
Suitable for partial laryngectomy	68	
Suitable for laryngectomy	111	
EXTRINSIC		133
Anterior Group (epiglottis, false cord, upper half of ary-epiglottic fold)	59	
Postero-Lateral Group (arytenoid, pyriform sinus, lower half of ary-epiglottic fold, post-cricoid)	40	
Extensive Group (both anterior and postero-lateral locations involved)	34	

In the laryngopharynx, we have found a marked difference in prognosis between the anterior lesions which include the epiglottis, false cords and upper half of the aryepiglottic folds, and the postero-lateral lesions which include the lower half of the aryepiglottic folds, arytenoids, pyriform sinuses and postcricoid region. Wherever possible the laryngopharyngeal lesions were classified into these two groups. However, there were extensive lesions which involved both anterior and posterolateral areas and such cases were classified separately as the extensive group.

PROGNOSIS

Briefly, the most important single factor in prognosis is involvement of the cervical lymph nodes which is dependent chiefly on the site of the primary tumor. Besides others, Pietrantoni has demonstrated this fact in his analysis of 465 consecutive cases of carcinoma of the larynx (Fig. 1).[4] He showed that only 0.4 per cent of cordal lesions had metastasis in lymph nodes, while in the extrinsic carcinomas metastasis could be demonstrated in the lymph nodes in 35 to 76 per

TABLE II

CARCINOMA OF INTRINSIC LARYNX TREATED BY IRRADIATION SUITABLE FOR PARTIAL LARYNGECTOMY

Total number of cases treated, 1931-1959		68
Cases for 5 year study, 1931-1954		43
Indeterminate (N.E.D. on last exam.)		9
Lost to follow-up	3	
Died from other causes	6	
Determinate cases		34
5 year survivals		30 or 88%
Absolute 5 year survival rate:		30/43 or 70%

cent of the cases depending on whether the site of the primary lesion is anterior or posterolateral. The presence of positive lymph nodes in radical neck dissection specimens has reduced greatly the chances of survival in all series reported. Thus, the need for radical neck dissection when nodes are present and even when they are not palpable in cases which offer a bad prognosis has become clear.[5-9]

CLINICAL MATERIAL AND RESULTS OF RADIATION THERAPY

From 1931 to 1959, 312 cases of carcinoma of the larynx and laryngopharynx were treated by irradiation. Of these, 179 were intrinsic and 133 extrinsic. Of the 179 intrinsic lesions, 68 were suitable for partial laryngectomy while 111 would have required total laryngectomy. Of the 133 extrinsic lesions, there were 59 in the anterior group, 40 in the posterolateral group and 34 in the extensive group (Table I).

Of the 68 cases of carcinoma limited to the vocal cord and suitable for partial laryngectomy, there were 43 treated from 1931 to 1954 and, therefore, available for five year study. Of these 43 cases, nine were indeterminate, three having been lost to follow-up and six having died from other causes, but all showed no evidence of disease when last seen. Of the 34 determinate cases, there were 30 five year survivals, a determinate survival rate of 88 per cent. If the indetermi-

TABLE III

CARCINOMA OF INTRINSIC LARYNX TREATED BY IRRADIATION SUITABLE FOR LARYNGECTOMY

Total number of cases treated, 1931-1959		111
Cases for 5 year study, 1931-1954		94
Indeterminate (N.E.D. on last exam.)		21
Lost to follow-up	10	
Died from other causes	11	
Determinate cases		73
5 year survivals		46 or 63%
Absolute 5 year survival rate:		46/94 or 49%

nate cases are regarded as failures, the absolute five year survival rate was 70 per cent (Table II).

Of the 111 cases of carcinoma of the intrinsic larynx that were suitable for laryngectomy, 94 were treated from 1931 to 1954 and, therefore, available for five year study. Of these 94 cases, 21 were indeterminate, 10 having been lost to follow-up and 11 having died from other causes. All indeterminate cases had no evidence of disease on the last examination. Of the 73 determinate cases, there were 46 five year survivals, a determinate survival rate of 63 per cent. If the indeterminate cases are regarded as failures, the absolute five year survival rate was 49 per cent (Table III).

Of the 59 cases of carcinoma of the extrinsic larynx in the anterior group, 53 were treated from 1931 to 1954 and, therefore, available for five year study. Of these 53 cases, eight were indeterminate, four having been lost to follow-up and four having died from other causes, all having shown no evidence of disease on the last examination. Of the 45 determinate cases, there were 25 five year survivals, a determinate survival rate of 56 per cent. If the indeterminate cases are regarded as failures, the absolute five year survival rate was 47 per cent (Table IV).

Of the 40 cases of carcinoma of the extrinsic larynx in the posterolateral group, 36 were treated from 1931 to 1954 and, therefore,

TABLE IV

CARCINOMA OF EXTRINSIC LARYNX TREATED BY IRRADIATION
ANTERIOR GROUP: Epiglottis, False Cord, Upper Half of Ary-Epiglottic Fold

Total number of cases treated, 1931-1959		59
Cases for 5 year study, 1931-1954		53
Indeterminate (N.E.D. on last exam.)		8
Lost to follow-up	4	
Died from other causes	4	
Determinate cases		45
5 year survivals		25 or 56%
Absolute 5 year survival rate:		25/53 or 47%

TABLE V

CARCINOMA OF EXTRINSIC LARYNX TREATED BY IRRADIATION
POSTERO-LATERAL GROUP: Arytenoid, Pyriform Sinus, Post-Cricoid, Lower Half of Ary-Epiglottic Fold

Total number of cases treated, 1931-1959		40
Cases for 5 year study, 1931-1954		36
Indeterminate (N.E.D. on last exam.)		8
Lost to follow-up	3	
Died from other causes	5	
Determinate cases		28
5 year survivals		9 or 32%
Absolute 5 year survival rate:		9/36 or 25%

available for five year study. Of these 36 cases, eight were indeterminate, three having been lost to follow-up, five having died from other causes, but all showed no evidence of disease on the last examination. Of the 28 determinate cases, there were only nine survivals, a determinate survival rate of 32 per cent. Again, if the indeterminate cases are regarded as failures, the absolute five year survival rate became 25 per cent (Table V).

TABLE VI

CARCINOMA OF EXTRINSIC LARYNX TREATED BY IRRADIATION
EXTENSIVE GROUP: Both Anterior and Postero-Lateral Locations Involved

Total number of cases treated, 1931-1959		34
Cases for 5 year study, 1931-1954		26
Indeterminate (N.E.D. on last exam.)		5
Lost to follow-up	1	
Died from other causes	4	
Determinate cases		21
5 year survivals		3 or 14%
Absolute 5 year survival rate:		3/26 or 11%

Finally, of the 34 cases of extrinsic laryngeal cancer in the extensive group, 26 were treated from 1931 to 1954 and, therefore, available for five year study. Of these 26 cases, five were indeterminate, one having been lost to follow-up and four having died from other causes, but all showed no evidence of disease on the last examination. Of the 21 determinate cases, there were only three five year survivals, a determinate survival rate of 14 per cent. With the indeterminate cases regarded as failures, the absolute five year survival rate was 11 per cent (Table VI).

RADIATION DOSAGE AND REACTIONS

Radiation therapy, naturally, has its share of risks and complications. With the older yet effective method of irradiation as administered with the 200-400 Kv x-ray machines, mucous membrane reactions and radiodermatitis of moderate intensity occurred regularly but usually healed completely. The most troublesome complication among our patients has been persistent laryngeal edema, particularly of the arytenoids. At present with the use of Cobalt-60 teletherapy, the skin manifestations are minimal, the mucous membrane reactions are slight to moderate in intensity, but postradiation edema of the arytenoids still occurs not infrequently. This edema very seldom jeopardizes the patient's airway but it may produce hoarseness.

TABLE VII

CARCINOMA OF THE INTRINSIC LARYNX
5 YEAR SURVIVAL RATES FOR PARTIAL LARYNGECTOMY

Frazell, 1960	171/190	90%
McGovran, Spjut, and Ogura, 1959	45/79	57%*
Pietrantoni and Fior, 1958	37/46	80%
Jackson, Blady, Norris, and Robbins, 1957	183/210	87%
O'Keefe, 1956	298/371	80%
Putney and Vicens, 1956	26/42	62%*
LeJeune and Lynch, 1955	172/203	85%
Schall, 1951	32/54	59%
TOTAL	964/1195	80%
M.S.H. radiation therapy	30/34	88%

* Absolute survival rate

It has been our experience that postradiation edema, when it occurs, usually disappears or is reduced to an insignificant minimum after a year or two. Corticosteroids and antibiotics are helpful in lessening the edema when there is a superimposed infection.

Persistent postradiation edema is related to the total dose, the overall time of its administration and the volume of tissue irradiated. It is greatly increased by infection. When deep ulceration affects the cartilage, the edema will be aggravated by chondritis. The extreme complication is sloughing of the cartilage, but this complication can be anticipated if exposed cartilage is noted or if chondritis is already present before radiation therapy is instituted. If cartilage is involved at the onset, laryngectomy is preferable to radiation therapy, except for the case in which only the tip of the epiglottis is affected.

Tumor doses in the range of 5000 to 7000 r have been administered over a period of five to eight weeks. The higher doses require the longer period of time and are applicable to the more advanced cases with the larger treatment field size. To reduce postradiation edema it is preferable not to exceed a dose range of 5500 to 6000 r in

TABLE VIII

CARCINOMA OF THE INTRINSIC LARYNX

5 YEAR SURVIVAL RATES FOR LARYNGECTOMY

O'Keefe, 1959	85/108	79%
Pietrantoni and Fior, 1958	31/62	50%
*Jackson, Blady, Norris, and Robbins, 1957	128/201	64%
Putney and Vicens, 1956	56/102	55%†
TOTAL	300/473	64%
M.S.H. radiation therapy	46/73	63%

*Includes epiglottis and false cords

† Absolute survival rate

five to six weeks and to keep the treatment field size to the minimum necessary for the known extent of the growth. This dose range is cancerocidal for almost all of the radiocurable cases of laryngeal cancer and it would not complicate any surgical procedure should one become necessary. Large doses of radiotherapy rarely succeed, but usually create conditions unfavorable to further surgery.

COMMENT

The objectives in the treatment of carcinoma of the larynx and laryngopharynx are first to save life, secondly to save the larynx and thirdly to save the voice.

In the most favorable group of cases which are the true cord lesions suitable for cure either by partial laryngectomy or by radiation therapy, the determinate survival rates for either modality have been between 80 and 90 per cent. A number of the recent surgical reports indicates an average five year survival rate of 80 per cent (Table VII).[10-17] The results in this group are excellent for saving life and there is no problem in saving the larynx. The choice of modality, therefore, is concerned with the factor of voice. In our opinion there is no question that radiation therapy yields by far the better voice.

In the more advanced intrinsic cancers which are treated either by laryngectomy or radiation therapy, the survival rates are over 60 per cent for either modality. A review of some of the recent results from

TABLE IX

CARCINOMA OF THE EXTRINSIC LARYNX
5 YEAR SURVIVAL RATES FOR LARYNGECTOMY
LESIONS OF EPIGLOTTIS AND FALSE CORD

Norris, 1959	28/49	57%
Pietrantoni and Fior, 1958	94/166	57%
Orton, 1956	73/122	60%
Clerf, 1952	19/34	56%
TOTAL	214/371	58%
M.S.H. radiation therapy	25/45	56%

laryngectomy shows an average five year survival rate of 64 per cent (Table VIII).[12,13,15,18] The radiation successes have the great advantage of preservation of the larynx and voice. We can expect improvement in these figures with the judicious employment of radical neck dissection as an elective procedure when indicated either as part of the surgical procedure or after radiation therapy. We wish to emphasize at this point that radiation failure may still be amenable to successful laryngectomy. We believe, however, that laryngectomy with radical neck dissection should be performed as a primary procedure when a small intrinsic lesion and palpable cervical lymph nodes exist.

In the special instance of true subglottic cancer, as distinguished from subglottic spread of a cord lesion, the results with either surgery or radiation therapy are poor. In these cases as well as in the advanced intrinsic carcinoma with palpable cervical lymph nodes it is our plan to employ the combined technique of radiation and surgery as will be described later.

There is an intermediate group of cases in which the growth is too extensive for partial laryngectomy but can be excised by hemi-laryngectomy. It is our opinion that such lesions are also suitable for radiation therapy.

In the laryngopharynx the growths which are located anteriorly and which involve the false cords, epiglottis or upper half of the ary-

TABLE X

CARCINOMA OF THE EXTRINSIC LARYNX
5 YEAR SURVIVAL RATES FOR SURGERY
LESIONS OF THE HYPOPHARYNX

Norris, 1959	9/30	30%
Pietrantoni and Fior, 1958	7/44	16%
Orton, 1954	11/66	17%
Clerf, 1952	6/12	50%
TOTAL	33/152	22%
M.S.H. radiation therapy	12/49	24%

epiglottic folds can be treated either by surgery or radiation with a survival rate of about 57 per cent. Recent reports of laryngectomy in this group of cases indicate an average five year survival rate of 58 per cent (Table IX).[12,19-21] About half of these cases also had simultaneous radical neck dissections. This group is similar to the advanced intrinsic group in management and prognosis. Here again improved results can be expected with the addition of elective radical neck dissections and successful surgical procedures for radiation failures.

The posterolateral group of laryngopharyngeal growths, namely cancer of the lower half of the aryepiglottic folds, arytenoids, pyriform sinuses and postcricoid lesions, present the most serious challenge to laryngeal surgeons and radio-therapists. These are the neoplasms which are frequently complicated by deep infiltration, fixation of the larynx and involvement of regional cervical nodes when seen for the first time. The general impression is that the results of surgery including radical neck dissections are better than with radiation therapy, but the fact is that the results are poor with either modality. These observations apply equally as well to the extensive group of laryngopharyngeal lesions in which both anterior and posterolateral anatomic sites are involved. Evidently it is the involvement of the posterolateral area which determines the poor prognosis of this group.

A survey of the literature shows that a relatively small number of cases were reported in this group. The average five year survival

rate for surgery was 22 per cent (Table X).[12,19,21,22] It is noteworthy, however, that Clerf reported a 50 per cent survival rate for 12 cases in nine of which a radical neck dissection was performed. Of six patients who survived, an elective procedure was done in four.

It is in this posterolateral group of laryngopharyngeal cancer that we believe that combined radiation therapy and radical surgery is indicated with the view to improve the survival rate of these desperate lesions. This kind of combined therapy has been initiated in clinics in Italy,[23] France[24-26] and lately in this country.[27] There are three different plans in which this combination is used: 1) surgery followed by radiation, 2) radiation given before and after surgery which accordingly has been called the sandwich method and 3) radiation followed by surgery.

We at The Mount Sinai Hospital have instituted an integrated program for this type of lesion in which radiation therapy is followed by radical surgery. With Cobalt-60 teletherapy it is possible to administer a tumor dose high enough to be in the cancerocidal range but not enough to interfere seriously with the surgical procedure. A tumor dose of 5500 r in five weeks is cancerocidal for the most actively growing cells which are usually located in the periphery of the lesion, in the lymphatics and in tissue planes. Three weeks after the completion of radiation therapy the reaction is practically healed. Surgery then should be performed between the third and sixth week after radiation. We have not observed any undue interference with wound healing. It is unfair to attribute all surgical complications to radiation therapy.

Although our experience with this form of combined therapy is limited thus far, we have been impressed by its efficacy. We have observed instances where the tumor seemed to have disappeared, where neoplasms which originally appeared formidable and possibly inoperable became amenable to surgery and where cervical lymph nodes, originally large and fixed, became smaller and more easily resectable. At times radiation therapy permitted a more thorough surgical extirpation.

When Kramer and Harris instituted radiation therapy for cancer of the larynx in 1931 in this country, it was regarded as a radical departure from the accepted methods of treating cancer of the larynx

of that period. It is probable that these ideas of combined therapy will evoke similar reactions in the minds of some laryngologists. However, we sincerely believe that the combined method of therapy is part of the evolutionary process of the treatment of this disease and will save many additional lives.

SUMMARY

Almost three and one-half decades of experience with radiation therapy at The Mount Sinai Hospital for carcinoma of the larynx has demonstrated that this is an effective method of treatment for this disease. The classification used was based on the prognosis predicated by the various anatomic sites of the larynx and laryngopharynx.

An 88 per cent determinate five year survival rate was obtained in carcinomas limited to the vocal cord and suitable for partial laryngectomy; a 63 per cent determinate survival rate in lesions of the intrinsic larynx suitable for laryngectomy; a 56 per cent determinate survival rate in carcinomas of the anterior group of the extrinsic larynx; a 32 per cent determinate survival rate in the posterior-lateral group of the extrinsic larynx; and a 14 per cent determinate survival rate in the extensive group of the extrinsic larynx.

The reported results with radiation therapy are compared with recent surgical statistics for laryngeal cancer. A program of combined radiation therapy and surgery for lesions which have a poor prognosis is suggested.

1050 Park Ave.

REFERENCES

1. Cantril, S. T.: Radiation Therapy in Cancer of the Larynx; A Review. Am. J. Roentgenol. 81:456-474, 1959.

2. Harris, W., Kramer, R., and Silverstone, S. M.: Roentgen Therapy for Carcinoma of the Larynx. Radiology 51:708-718, 1948.

3. Harris, W., Silverstone, S. M., and Kramer, R.: Roentgen Therapy for Cancer of the Larynx and Laryngopharynx. Am. J. Roentgenol. 71:813-825, 1954.

4. Pietrantoni, L.: Il problema chirugico delle metastasi lingoghiandolari de cancro della laringe. Arch. Ital. Otol. Suppl. 14, 64:1-37, 1953.

5. Ogura, J. H., and Bello, J. A.: Laryngectomy and Radical Neck Dissection for Carcinoma of the Larynx. Laryngoscope 62:1-52, 1952.

6. Clerf, L. H.: Evaluation of Dissection of the Neck in Carcinoma of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 64:451-456, 1955.

7. O'Keefe, J. J.: Secondary Radical Neck Dissection. Laryngoscope 65:136-141, 1955.

8. Putney, F. J.: Preventive Dissection of the Neck in Cancer of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:136-147, 1958.

9. Reed, G. F., Mueller, W., and Snow, J. B., Jr.: Radical Neck Dissection; A Clinico-Pathological Study of 200 Cases. Laryngoscope 69:702-743, 1959.

10. Frazell, E. L.: Personal Communication.

11. McGavran, M. H., Spjut, H. J., and Ogura, J.: Laryngofissure in the Treatment of Laryngeal Carcinoma. Laryngoscope 69:44-53, 1959.

12. Pietrantoni, L., and Fior, R.: Clinical and Surgical Problems of Cancer of the Larynx and Hypopharynx. Acta Otolaryng., Stockholm, Suppl. 142, pp. 1-61, 1958.

13. Jackson, C. L., Blady, J. V., Norris, C. M., and Robbins, R.: Carcinoma of the Larynx. J.A.M.A. 163:1567-1570, 1957.

14. O'Keefe, J. J.: The Surgery of Cancer of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 65:131-136, 1956.

15. Putney, F. J., and Vicens, E. A.: Surgical Treatment of Carcinoma of the Anterior Commissure of the Larynx. Laryngoscope 66:1041-1058, 1956.

16. LeJeune, F. E., and Lynch, M. G.: The Value of the Laryngofissure Operation. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 64:256-262, 1955.

17. Schall, L. A.: Symposium: Carcinoma of the Larynx. Five Year Results. Laryngoscope 61:517-522, 1951.

18. O'Keefe, J. J.: Concerning the Criteria of Operability in Laryngeal Cancer. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 68:453-460, 1959.

19. Norris, C. M.: Causes of Failure in Surgical Treatment of Malignant Tumors of the Larynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 68:487-508, 1959.

20. Orton, H. B.: Surgery of Carcinoma of the Larynx. A.M.A. Arch. Otolaryng. 64:205-206, 1956.

21. Clerf, L. H.: Proceedings of the Second National Cancer Conference, New York City, American Cancer Society, Vol. 1, p. 462, 1952.

22. Orton, H. B.: Symposium: Carcinoma of the Larynx. Tr. Am. Acad. Ophth. 58:30-34, 1954.

23. Pietrantoni, L.: Personal Communication.

24. Leroux-Robert, J., et Ennuyer, A.: Cancer du Sinus Piriforme. Extrait du Rapport au Le Congres Francois d'Oto-Rhino-Laryngologie, Paris, 1952.

25. Leroux-Robert, J.: Indications for Radical Surgery, Partial Surgery, Radiotherapy, and Combined Surgery and Radiotherapy for Cancer of the Larynx and

Hypopharynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 65:137-153, 1956.

26. Romieu, C., Pourquier, H., Leenhardt, P., Gary-Bobo, J., Pages, A., and Pujol, H.: Telecobalt Therapy of Cervical Lymph Node Metastases. J. de radiol. et d'électrol. 39:369-377, 1958.

27. MacComb, W. S., and Fletcher, G. H.: Planned Combination of Surgery and Radiation in Treatment of Advanced Head and Neck Cancers. Am. J. Roentgenol. 77:397-414, 1957.

LXVI

EXTRAMEDULLARY PLASMACYTOMA OF THE UPPER AIR PASSAGES

JULIUS W. MCCALL, M.D.

CARL H. BAILEY, JR., M.D.

CLEVELAND, OHIO

Plasmacytomas are rare tumors found usually in the upper respiratory passages, although their occurrence has been recorded in other parts of the body. There have been approximately 200 cases of plasmacytoma reported in the literature.

The cellular make-up of these tumors is identical with that of multiple myeloma. This tumor was first described by Schridde[1] in 1905.

Microscopically the plasma cells which compose a majority of the tumor have abundant cytoplasm and are of variable size, elliptical in shape, with eccentric nuclei having a spoke-like configuration of the chromatin material. The cytopalsm may stain in either a basophilic or neutrophilic fashion.

There were no mitotic figures seen in the microscopic examinations of our series, but this is not considered to be a criterion of malignancy in the disease. Rawson, Eyler and Horn[2] emphasize that malignant cell tumors may not show the usual cytologic characteristics of malignancy, and they point out that such criteria, if found in considerable degree, may be regarded as reliable diagnostic evidence. They believe that the replacement of tissue by broad sheets of plasma cells arranged in a delicate capillary stroma is definitely indicative of a malignant tumor and that the absence of this problem makes malignancy unlikely.

We did not encounter excessive bleeding in the surgical management of these individuals. Clyde Heatly,[3] who reported 2 cases of

plasmacytoma of the maxillary sinus, before this Association in 1953, was impressed by the tremendous vascularity of the antral tumor. The bleeding in one of his cases necessitated ligation of the external carotid artery. Lumb and Prosser[4] had a similar experience and concluded that the vascularity of the plasmacytoma in the maxillary sinus tends to be greater than those occurring elsewhere.

INCIDENCE AND AGE

This disease is less common in females than in males. In our five cases, all were males. All writers agree that most of these tumors occur in males after the age of 40; the age range in our group was 41 to 70 years.

Plasmacytomas usually appear as solitary tumors, but occasionally they may be multiple. Hellwig, Stout and Kinney, Blacklock and McCartney, and Mattick and Priest[1,5-8] have all reported cases of multiple tumor.

SIGNS AND SYMPTOMS

Plasmacytoma is such a rare tumor it is seldom considered in a differential diagnosis; the diagnosis is usually established by the microscopic examination of the tissues removed. In two of our cases obstruction was the predominant symptom; in two it was a mass; and in one it was diplopia and headache.

The tumor appears grossly as a soft, friable, pale gray mass with varying amounts of red, depending upon the amount of hemorrhage and necrosis present.

DIFFERENTIAL DIAGNOSIS, PLASMACYTOMA, MULTIPLE MYELOMA

Many pathologists feel that there is no line of differentiation between plasmacytoma and multiple myeloma. Multiple myeloma is a systemic disease of the bone marrow and is more common in people past 40 years of age. The symptoms are usually vague and are characterized by muscular pain and weakness. Often the osteolytic lesions lead to pathologic fractures. Laboratory findings usually include Bence-Jones proteinuria, normochromic anemia, elevated globulins

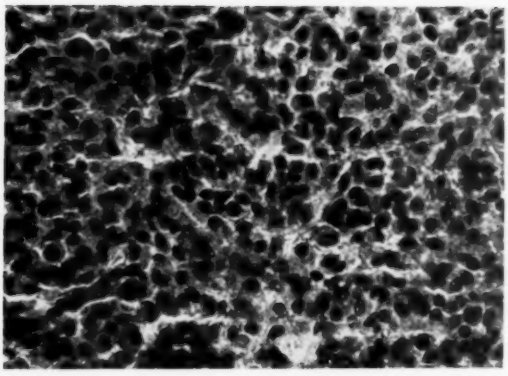

Fig. 1.—The plasma cells are elliptical in shape and variable in size. The nuclei, eccentrically located, have a spoke-like configuration of chromatin material. No mitotic figures were seen in this series.

in the plasma proteins and normal serum phosphates. The diagnosis is established by bone marrow aspiration showing an excessive number of myeloma cells.

Punched-out lesions, especially in the spine, skull, shoulder, and pelvis are characteristically seen on skeletal x-ray.

The histology of plasmacytoma is identical with that of multiple myeloma. Plasmacytomata seldom metastasizes to distant organs. If lesions appear in other parts of the body, these are probably multicentric primary foci rather than metastases. However, local extension to adjacent structures does occur.

TREATMENT

These tumors being lymphogenous in nature should be radio sensitive. The tumors in two of our group responded to irradiation.

In the patient with subglottic plasmacytoma the possibility of causing chondritis of the laryngeal cartilages, or severe respiratory distress prompted us to remove this tumor surgically. Heatley[3] sug-

Fig. 2.—This illustration shows the location of the tumor by indirect laryngoscopy.

gests that pedunculated tumors are best treated by removal and cautery of the base. If massive surgery is required to remove the tumor irradiation should be the treatment.

REPORT OF CASES

CASE 1. B.M. This 58-year-old white male was admitted on February 24, 1957, because of a lump in the lower jaw of one month's duration.

Physical examination was not remarkable except for a 3 cm mass of the right lower alveolar ridge. Excisional biopsy was made with a histologic diagnosis of plasmacytoma.

The urine was negative for Bence-Jones proteins, total protein of 6.6, albumin-globulin ratio 1.5. The skeletal survey and gastrointestinal x-rays were reported as normal as was the bone marrow aspiration.

On March 4, 1957, the patient was returned for surgery. The adjacent margin of the mandible and soft tissue was excised leaving the inferior rim of the mandible intact.

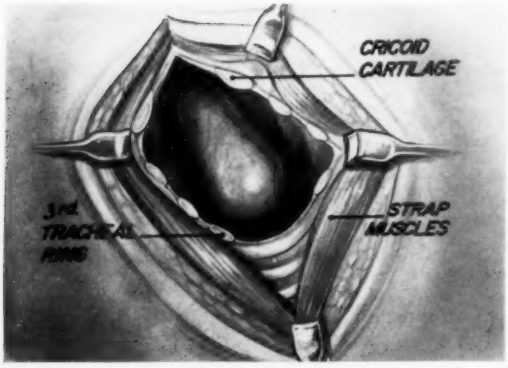

Fig. 3.—The tumor as it appears in the lumen of the trachea with anatomic relationships noted.

The patient did well until September, 1957, when a mass again became evident in the same area. The right ramus of the mandible was excised and an ipsilateral supraomohyoid dissection was performed. A tantalum plate was inserted in the surgical defect.

The patient has had no exidence of recurrence or metastasis and was last seen November, 1959.

CASE 2. G.V. This 70 year old white male was first seen on May 20, 1955, complaining of nasal obstruction and postnasal drip. Physical examination revealed a red granular mass obstructing the left naris. X-ray examination revealed a soft tissue density of the left ethmoid and maxillary sinuses. Nasal polypectomy and intranasal ethmoidectomy were done. An excision of the left middle and inferior turbinates was carried out at the same time. Histologic examination revealed plasmacytoma.

Laboratory studies which followed revealed the urine to be negative for Bence-Jones protein. Serum protein was 6.6. Albumin-globulin ratio was 0.6. The skeletal survey was negative.

The patient was seen only erratically following this procedure and in May of 1957, the patient returned complaining of blocking of the

Fig. 4.—The surgical appearance of the pedunculated tumor after the cricoid cartilage has been severed.

right naris. Further therapy was advised but the patient was not again seen at our hospital.

Follow-up of the patient reveals that he presented himself at another institution complaining of nasal obstruction. Physical examination revealed obstruction of both nares by tumor masses.

X-ray therapy was begun September 18, 1957. Examination on September 26, 1957, showed the tumors to be reduced in size. X-ray therapy was completed October 4, 1957. He received a total dosage of 1500 R.

Examination on November 12, 1957, showed no further reduction in size of the tumors. On December 27, 1957, cobalt therapy was instituted and directed to the nasopharynx. An estimated tumor dose of 4000 R was given. The patient was next seen on February 3, 1958, at which time there was no change in the size of the masses. No further treatment was given. In October, 1958, the patient developed painless jaundice.

A diagnosis of carcinoma of the pancreas was made. He died of this disease in August, 1959. There was no autopsy performed but there was tumor present in his nose at this time.

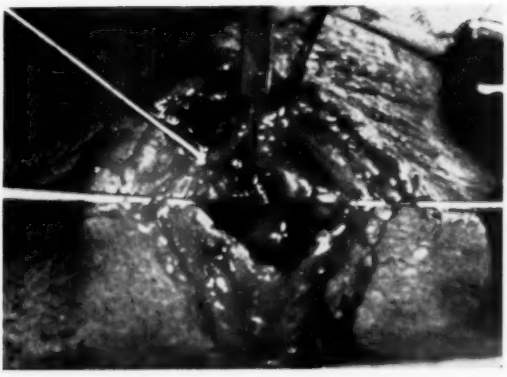

Fig. 5.—The nasal snare being applied to the base of the growth.

CASE 3. P.M. This 60 year old white male was admitted on January 27, 1954, for investigation of bony abnormalities discovered by dental x-ray. Physical examination revealed a slight prominence of the left maxillary and zygomatic areas with minimal tenderness on palpation. Examination of the alveolar ridge on this side revealed a fistulous tract to the maxillary sinus. X-ray showed the destruction of the medial, lateral, and superior margins of the left maxillary sinus, and soft tissue densities in the ethmoid labyrinth on the left side. Using a Caldwell-Luc approach a trans-antral ethmoidectomy and sphenotomy were done on January 30, 1954. A diagnosis of plasmacytoma was made.

Laboratory data following this showed the urine to be negative for Bence-Jones protein, serum protein to be 8.2, albumin 3.7, AG ratio 0.8. The bone marrow aspiration was normal.

Between April 6, 1954 and April 29, 1954, the patient received a total of 9200 R (air dose) to the left antral and orbital areas. In October, 1954, the patient developed a pathologic fracture to the left tibia. He received 3600 R to this area. In March, 1955, he developed a bony lesion of the left elbow for which he was given 3600 R. The following year the patient developed lesions of the lower lip and nose for which he received a total 9900 R. He died September 9,

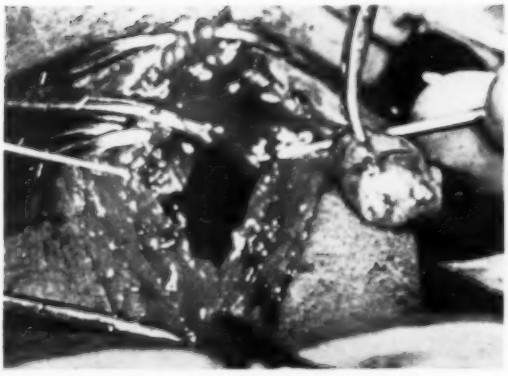

Fig. 6.—The specimen is seen to the right, the tracheal lumen is clear with minimal bleeding.

1956, apparently of this disease. No autopsy was performed. In retrospect this was probably plasmacytoma in its inception; however, the late clinical course of this disease was that of multiple myeloma.

CASE 4. F.K. This 60 year old white male was admitted on August 22, 1955, with the chief complaint of increasing frontal headache of five months' duration and intermittent displopia of six weeks' duration.

Physical examination revealed only paresis of the right lateral rectus muscle. X-ray revealed a bony destruction of the floor of the sella turcica and a soft tissue mass filling the posterior two-thirds of the right sphenoid sinus.

On September 5, 1955, the right sphenoid was explored transnasally and a biopsy was taken. The Pathology Department described the specimen as an unclassified soft-tissue tumor. On September 19, 1955, another transnasal exploration and biopsy were done. At this time the diagnosis of plasmacytoma was made. Laboratory studies revealed the urine to be negative for Bence-Jones protein. The bone marrow aspiration was normal.

The patient received x-ray therapy from September 27 to October 12, 1955, of 4500 roentgens from four external portals.

The patient was last seen in November, 1959, at which time there was no clinical evidence of recurrence.

CASE 5. C.T. In April, 1953, this 41 year old white male was seen because of the voice change of six months' duration. He denied weight loss, dyspnea or memory of a preceding respiratory infection.

Physical examination revealed no significant abnormalities except a small red mass in the anterior commissure. Direct laryngoscopy and excision of the mass were performed and the diagnosis of plasmacytoma was established histologically.

The patient moved to another section of the country and was not seen again until January 3, 1959, when he returned complaining of moderate dyspnea and some recent voice change. A similar lesion just below the left true vocal cord was seen and biopsied. Microscopic sections were identical with those examined in 1953.

No further therapy was permitted until September 16, 1959, when he returned with marked dyspnea.

Laryngoscopy revealed no apparent involvement of the true cords, but a pedunculated tumor, apparently arising from the subglottic wall posteriorly which occluded more than half the diameter of the trachea. It was then decided to approach the tumor externally.

The first three tracheal rings were divided as well as the cricoid cartilage to adequately visualize the mass. It was attached by a short stalk to the posterolateral wall at the level of the cricoid cartilage. A wire snare was used to remove the mass and the base was cauterized. Bleeding was minimal. The postoperative course was uneventful.

Throughout the entire period laboratory studies, including Bence-Jones proteins, serum proteins, bone marrow aspiration, albumin-globulin ratio, skeletal surveys, and electrophoretic studies were normal. When last seen on January 10, 1960, there was no evidence of recurrence.

THERAPY AND OUTCOME

Of this group two were treated surgically without irradiation. One was treated by irradiation only. Two received both surgery and irradiation.

The two receiving surgical therapy are alive. The patient with plasmacytoma of the mandible has survived three years without evidence of recurrence.

The individual with plasmacytoma of the larynx has survived seven years since the recognition of the original tumor, but its recent reappearance in the larynx precludes evaluation of this therapy.

The patient with sphenoid plasmacytoma who received only irradiation has survived four and a half years without evidence of recurrence.

The other patient with primary maxillary sinus involvement developed multiple bony and soft tissue lesions. He succumbed to the disease within two and a half years after diagnosis.

It appears that the clinical course of plasmacytomas cannot be predicted from histopathological examination.

CONCLUSIONS

There is a close relationship between plasmacytoma and multiple myeloma. Indeed, multiple myeloma may be a progression of plasmacytoma. These tumors being of lymphatic origin should be and usually are radiosensitive. Irradiation should be the treatment of choice unless the tumor is pedunculated.

No individual or institution sees enough patients with this disease to qualify as an authority in its management.

610 Rose Bldg.

We are indebted to Mr. William M. Holmes for the illustrations.

REFERENCES

1. Hellwig, C. A.: Extra Medullary Plasma Tumors as Observed in Various Locations. Arch. Path. 36:95, 1943.

2. Rawson, A. J., Ailer, P. W., and Horn, R. C., Jr.: Plasma Cell Tumors of the Upper Respiratory Tract: a Clinico-Pathologic Study with Emphasis on Criteria for Histologic Diagnosis. Am. J. Path. 26:445, 1950.

3. Heatly, C. A.: Primary Plasma Cell Tumors of the Upper Air Passages with Particular Reference to Involvement of the Maxillary Sinuses. Trans. Am. Laryn. Assn. 74:52, 1953.

4. Lumb, G., and Prosser, T. M.: Plasma Cell Tumors. J. Bone and Joint Surg. 30-B:124, 1948.

5. Stout, A. P., and Kenney, F. R.: Primary Plasma Cell Tumors of the Upper Air Passages and Oral Cavity. Cancer 2:261, 1949.

6. Blacklock, J. W. S., and MacArtney: Plasmacytoma of the Nasopharynx. J. Path. and Bact. 35:69, 1932.

7. Mattick, W. L.: Plasmacytoma, an Unusual Case with Progressive Involvement of Waldeyer's Ring and the Larynx, Bronchus and Pleura. Arch. of Otolaryngology 51:263, 1950.

8. Priest, R. E.: Extra Medullary Plasma Cell Tumors of the Nose, Pharynx and Larynx. Trans. Am. Laryn., Rhin. and Otol. Soc., Inc. 278, 1952.

ADDITIONAL BIBLIOGRAPHY

Parks, M., and Burtoff, S.: Plasma Cell Tumor Simulating Bilateral Maxillary Sinusitis. Arch. Otolaryngology 50:666, 1949.

Fuerste, F., Jr., and Zuckerman, S. S.: Extra Medullary Plasma Cell Tumor. Arch. Otolaryngology 51:608, 1950.

Eggston, A. A., and Wolff, D.: Histopathology of the Ear, Nose and Throat. Baltimore, Williams and Wilkins Co., p. 778, 1947.

Connor, C. E.: Solitary Extra Medullary Plasmacytoma: Case Report. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 55:342, 1946.

Ash, J. E., and Raum, M.: An Atlas of Otolaryngic Pathology. Amer. A.M. Registry of Pathology, p. 237, 1949.

Chase, W. D.: Solitary Myeloma Mistaken for Frontal Sinusitis. Arch. Otolaryngology 48:244, 1948.

Moguda, R. A., and Maiden, S. D.: Plasmacytoma of Nasal Cavity. Arch. of Otolaryngology 51:258, 1950.

Shea, J. S.: Pathology of Nasal Polyps and Related Growths. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 56:1029, 1947.

Switzer, P. K., and Moseley, V., and Cannon, W. M.: Extra Medullary Cytoma Involving Pharynx, Skin and Lymph Nodes. Arch. Int. Med. 86:402, 1950.

Waltner, J. G.: Plasma Cell Tumors of Nasopharynx. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 56:911, 1947.

Cecil, R. L., and Loeb, R. F.: A Textbook of Medicine. Philadelphia, W. B. Saunders Co. 2:1113.

Ewing, M. R., and Foote, F. W., Jr.: Plasma Cell Tumors of the Mouth and Upper Air Passages. Cancer 5:499, 1952.

Figi, F. A., and Broders, A. C., and Havens, F. Z.: Plasma Cell Tumors of the Upper Part of the Respiratory Tract. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 54:283, 1945.

Greenfield, M. M.: Malignant Plasmacytoma of the Nasopharynx. A Case of Multiple Myeloma Primary in the Nasopharynx. Radiology 501:661, 1948.

The Scientific Papers of the American Otological Society

(Continued)

LXVII

INNER EAR PATHOLOGY IN DEAFNESS DUE TO MUMPS

J. R. Lindsay, M.D.

Patricia R. Davey, F.R.C.S. (Ed.)

and

Paul H. Ward, M.D.

Chicago, Ill.

Deafness due to the mump virus is a well known, and not infrequent, accompanying manifestation of epidemic parotitis. Although a number of cases are seen each year in large otolaryngologic clinics and many cases have been reported, we were unable to find any reports in the literature of previous histopathological study of either the temporal bones or the VIII nerve, in an autopsied case of mumps deafness. The pair of temporal bones to be described in this report were removed from a patient who had acquired bilateral deafness due to mumps.

Mumps as a disease entity was known and described by Hippocrates,[1] who wrote of an epidemic on the island of Thasos in the 5th century B.C. He also called attention to the occurrence of orchitis

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From the Section of Otolaryngology of the University of Chicago.

The cost of the laboratory work was defrayed in part by a grant from the Central Bureau of Research of the American Otological Society Inc.

during this epidemic. In 1790, Hamilton[2] again recorded the parotid and testicular involvement and observed the rather frequent central nervous system manifestations.

Much speculation was advanced as to the cause of mumps, but it was not until the brilliant work of Johnson and Goodpasture[3] (1934) that the filterable virus was isolated, transmitted and reisolated thereby establishing the etiology. During the past century involvement of many other organs and glands have been reported including salivary glands, testis, lacrimal glands, thyroid, thymus, ovaries, pancreas, Bartholini's glands, myocardium, mammary glands, kidneys, labyrinth and the central and peripheral nervous system. This multiple organ involvement makes it imperative that mumps be considered a systemic disease, rather than parotitis with complications. The occurrence of orchitis, meningitis, labyrinthitis or other organ involvement, in association with or even in the absence of clinical parotitis, implies a severity of involvement of that particular part of the body.

The use of serological tests to identify the mumps virus as the etiological agent in cases of aseptic meningitis,[4] with or without parotitis, supports this concept. Studying the routine spinal fluids from 372 cases with mumps, Bang and Bang[5] recorded a pleocytosis in 63%. Of these, 106 manifested meningeal symptoms, while in 129 the increase in cells in the spinal fluid was the only evidence of an occult meningeal involvement. The estimated incidence of meningeal involvement has varied, from epidemic to epidemic, and from author to author, with a range of 3 to 100%. Some believe the initial malaise and febrile period represents central nervous system or systemic invasion by the virus, which is subsequently followed by parotitis.[6]

The occurrence of deafness accompanying epidemic parotitis was mentioned by Hintz,[7] in 1803, and reported in more complete form by Toynbee in 1860 in his monumental work, "The Diseases of the Ear."[8] It was said that he dissected over 1000 temporal bones. In our review of the literature, he appeared to be the only person to have recorded a gross dissection of a temporal bone in a case of mumps deafness. He described a complete disorganization of the nervous apparatus and dark fluid in the vestibule and cochlea.

Since Toynbee's description of deafness in mumps there has been much speculation, and oftentimes, heated argument, over the possible

pathological changes which could explain the deafness. The various hypotheses advanced were, occlusion of the internal auditory artery or its branches, neurolabyrinthitis, meningoradiculitis,[9-13] labyrinthitis,[14-16] and endolabyrinthitis.[17] None of these has been confirmed by examination of necropsy material.

The pathological material from other organs has shown changes which demonstrate the type of destruction that the virus is capable of causing. Gross and microscopic descriptions of involved human salivary glands have shown edema of the tissue surrounding the gland, petechial hemorrhages in the capsule and scattered diffusely throughout the gland and disintegration of the acinar cells some of which contain cytoplasmic inclusion. There has been prominent periductal and perivascular mononuclear cell infiltration, marked interstitial edema and degeneration of the ductal epithelium. Studying the histopathology of mumps in the salivary gland of monkeys Johnson and Goodpasture[18] confirmed the presence of edematous periglandular tissue, petechial hemorrhages, and marked edema. They describe microscopic changes of both a diffuse and focal nature. There was diffuse widening of the interlobular and interacinar spaces by serofibrinous exudate, edema of the acinar cells and generalized damage to the vascular bed. The focal changes observed consisted of destructive changes in acinar cells with mononuclear cell infiltration in these injured areas and about the ducts and vessels. The hemorrhages were fresh interstitial extravasations of blood, frequently not associated with the focal areas of necrosis.

In the testes damage to the vascular bed was demonstrated by the profuse edema in the interstitial connective tissue and numerous areas of petechial hemorrhage. The process was not uniform, for while many of the seminiferous tubules showed complete destruction and were filled with exudate others were only slightly involved.[19,20] The edematous distention within the limiting capsule undoubtedly contributed to additional damage.

The pathological findings in the few published cases of fatal mumps meningitis were summarized by Everberg (1957).[21] The meninges were said to have been thickened by serofibrinous exudate with localized fibrinous plaque-like areas and a gelatinuous edema surrounding the nerves and base of the brain.

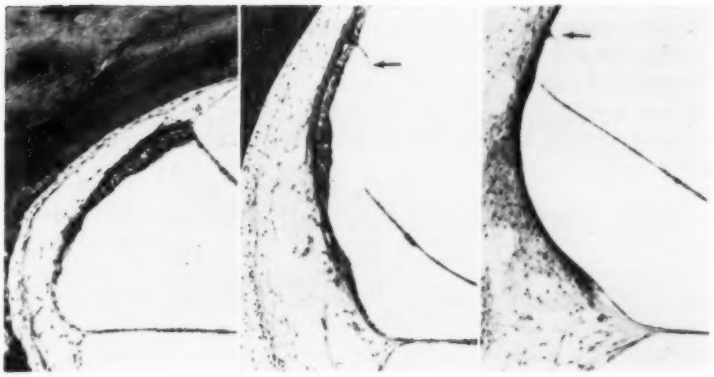


Fig. 1.—Photomicrographs showing the stria vascularis at the middle region of the apical A, middle B, and basal coils C of the left ear. Arrows indicate torn Reissner's membrane at the upper end of the stria (artifact).

CLINICAL PICTURE

The onset of the deafness in mumps may be dramatic, especially in bilateral cases, or may be unnoticed for years in the very young unilateral cases. It is usually rapid in onset and unilateral but may be bilateral. Males and females are involved about equally. The loss of hearing may occur before, during or after the parotitis or in its apparent absence. It may also occur with or without obvious meningeal involvement. Little relationship has been noted between the severity of other manifestations of the disease and the occurrence of deafness.

Tinnitus and a sensation of fullness may call attention to the involvement of the ear. The audiogram usually shows a severe to complete perceptive type hearing loss. Not infrequently there may be some perception of sound for frequencies at and below 512 cps despite masking of the good ear by 100 db of white noise. The loss of hearing is nearly always permanent. A small minority of cases have vertigo, nausea and vomiting. If there has been vestibular involvement the reaction to caloric stimulation may be diminished or, as in one case recently observed by us the response may be absent.

The incidence of deafness due to mumps is difficult to ascertain, since many unilateral cases in young children remain undetected for years. Bang and Bang[5] found one case of deafness in 372 cases of mumps. In a series of 296 cases of deafness in children and adolescents, using P.G.S.R. tests when necessary, Bordley and Hardy[22] found only one case attributable to mumps. They recognized that many of the younger children in the series may not have been exposed to the disease.

Boat[14] reported the incidence in males and females to be similar but found bilateral involvement in ten of 51 cases collected from the literature while Everberg[21] in 1957 also found a bilateral incidence of over 20 per cent. The exact proportion of bilateral cases seen at this institution is not presently known but while several unilateral cases have been seen annually for many years bilateral occurrence has been rare.

It was estimated by Hubbard[15] that 3 to 5% of deafmutes in the United States were due to mumps. Everberg[21] believed this figure to be too high and estimated deafness to occur as a "complication" of mumps in 0.05 cases per thousand, which would indicate the proportion of deafmutism caused by mumps to be closer to 1 per cent.

The histopathological findings in the inner ears of the well authenticated case to be presented here is of special interest since a careful search of the literature has not disclosed any other such report up to the present.

REPORT OF A CASE

In December 1950 the two five-year-old twin siblings of the patient contracted mumps. Later in December the patient, aged 28 months, and his three-year-old sister also developed parotid swelling and were confined to the house over the holidays, at the request of the visiting doctor. The parotid swelling and malaise of the siblings subsided in a few days but the patient seemed to have a prolonged course. On New Year's day 1951 the parents found that he was totally unable to hear. All efforts to "test and try him in many different ways" were to no avail. The attending physician after a week of observation referred the parents and the child to a specialist who confirmed the presence of the profound hearing loss and informed the parents that the prognosis for recovery of the boy's hearing was poor.

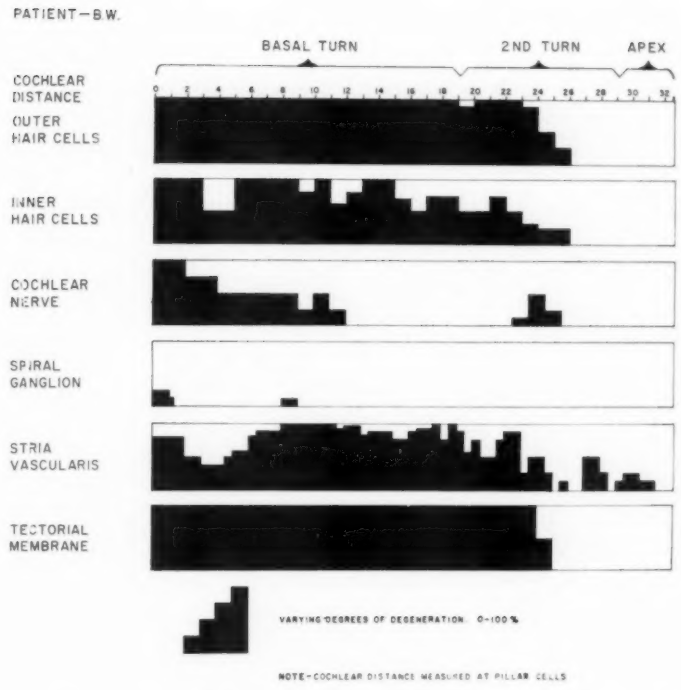


Fig. 2.—Chart of the left cochlea. The black areas represent the estimated degree of degeneration of the various parts.

Prior to the illness the patient was described by the parents as "a normal healthy body, probably the brightest of the four children." His speech had been good and he had been using sentences. Within six months his speech had deteriorated greatly.

From this illness until his death at the age of 6 years, he remained alert, but suffered from nephritis with almost constant hematuria. The terminal illness was of rather sudden onset, progressing rapidly into coma and death. An autopsy was granted, at which both temporal bones were removed, preserved in formalin and brought to the University of Chicago by one of the authors (F.D.). The final patho-

logical diagnosis and cause of death after microscopic examination was reported as inclusion cell encephalitis.

The temporal bones were sectioned at 20 microns and every tenth section was stained with hematoxylin and eosin.

The cochlear and vestibular structural changes were studied, plotted and graphically illustrated, according to the method described by Guild[23] and modified by Schuknecht.[24]

LEFT TEMPORAL BONE

Middle Ear. The middle ear showed well preserved mucosa with no evidence of old or recent infection. The ossicles and tympanic membrane were in good condition.

Labyrinthine Capsule. No abnormalities were noted in the bony labyrinthine capsule.

Inner Ear. The membranous structures were well preserved. Some early postmortem degenerative changes were present.

Perilymphatic Spaces. The scala tympani, scala vestibuli, and scala media were free of any debris or precipitate. The delicate supporting connective tissue trabeculae and small blood vessels in the perilymphatic space of the semicircular canals were normal.

Endolymphatic System. Cochlear Duct. The volume of endolymph appeared normal with no distortion of Reissner's membrane except for a few isolated areas where it was torn (artifact). In a few areas a small amount of debris appeared attached to Reissner's membrane.

Stria Vascularis. There was almost complete absence of the stria vascularis in most of the basal, and part of the middle coils. The degree of atrophy decreased more or less progressively up through the middle and apical coils, approximately one fourth being absent at the apex. The atrophy involved that part of the stria adjacent to the spiral eminence (Figs. 1 and 2). There was no evidence of recent inflammatory reaction.

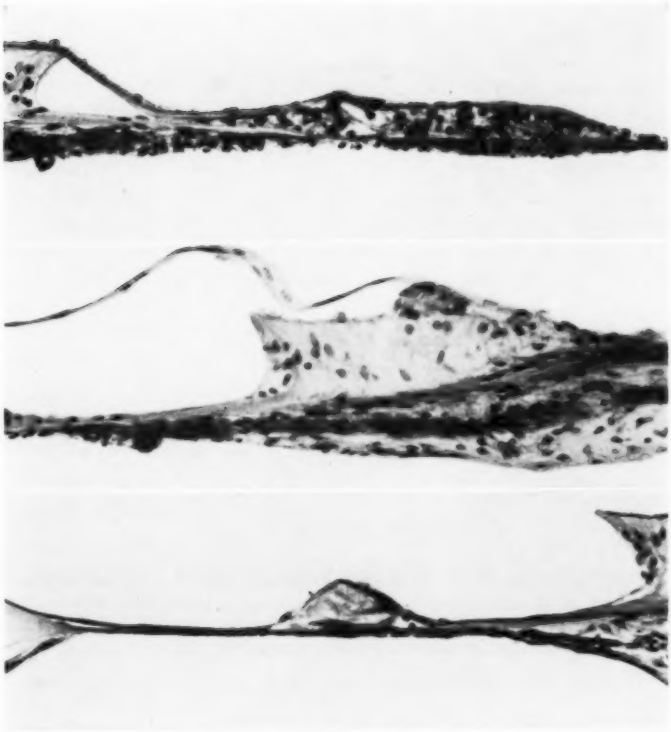


Fig. 3.—Photomicrographs showing the remnants of the tectorial membrane in the apical A (top), middle B and basal coils C of the left ear. The organ of Corti is absent in the basal coil B but is present in the apical coil A. Although depressed and distorted the pillars are present and the hair cell nuclei can be distinguished.

Tectorial Membrane. Degenerative changes were present throughout all coils. In the basal and part of the middle coil the tectorial membrane was detached from the limbus spiralis and appeared as a hyaline mass surrounded by a single layer of flattened cells. This mass was situated on the basilar membrane in the area of the degenerated, or completely absent organ of Corti. Further toward the apex

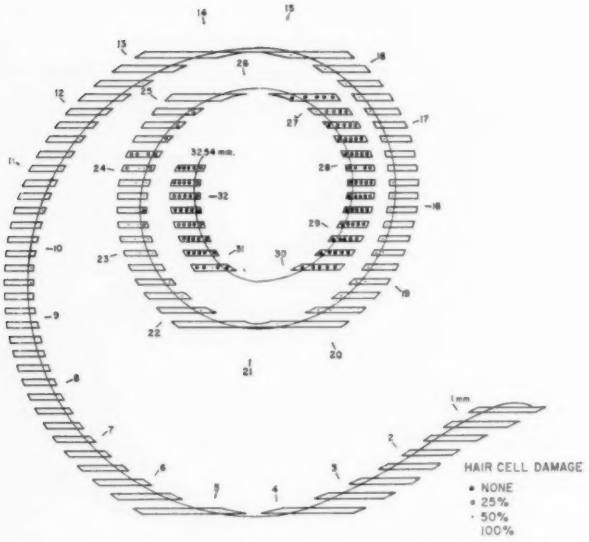


Fig. 4.—Graphic reconstruction of the organ of Corti of the left ear. Although normal numbers of hair cells nuclei could be distinguished in most regions of the apical coil, the distortion of the pillars, hair cells and tectorial membrane were considered as indicating early degenerative change.

it was rolled up on the surface of the limbus and covered by flat epithelial cells near the attachment of Reissner's membrane (Fig. 3). In the apical region the tectorial membrane was flattened out but lay over the partly degenerated organ of Corti.

Organ of Corti. There were degenerative changes throughout all coils. These varied progressively from complete absence in the basal coil to a moderate degree of degeneration in the apical coil. In the upper middle and apical coils the hair cells were present in nearly normal numbers as indicated by the nuclei. Throughout this area however there was moderate depression of the organ of Corti with the tectorial membrane flattened out and still attached (Fig. 3A). These changes limited to the more distal part of the organ were interpreted as indicating early degenerative change (Figs. 4 and 2). The graph (Fig. 2) demonstrates parallel areas of degenerative change

in the stria vascularis, hair cells of the organ of Corti and the tectorial membrane.

Nerve and Ganglion. There were normal numbers and distribution of the nerve fibers and ganglion cells in the apical and middle coils. In the basal coil nerve fibers showed some apparent decrease in numbers in the lower half, the decrease becoming more definite at the proximal end. The ganglion cells supplying the basal coil showed some diminution in number, and some asymmetry in distribution. The difficulty encountered in evaluation of the ganglion cell degeneration in this area makes quantitative evaluation unreliable.

Vestibular System. Preservation of the membranous vestibular system was good. The utricle, saccule and membranous semicircular canal appeared normal. The maculae of the saccule, utricle and the sensory epithelium of the canals showed only postmortem autolytic changes. The semicircular canals, ampullae, cristae and remnants of the attached cupulae of all three canals appeared normal.

RIGHT TEMPORAL BONE

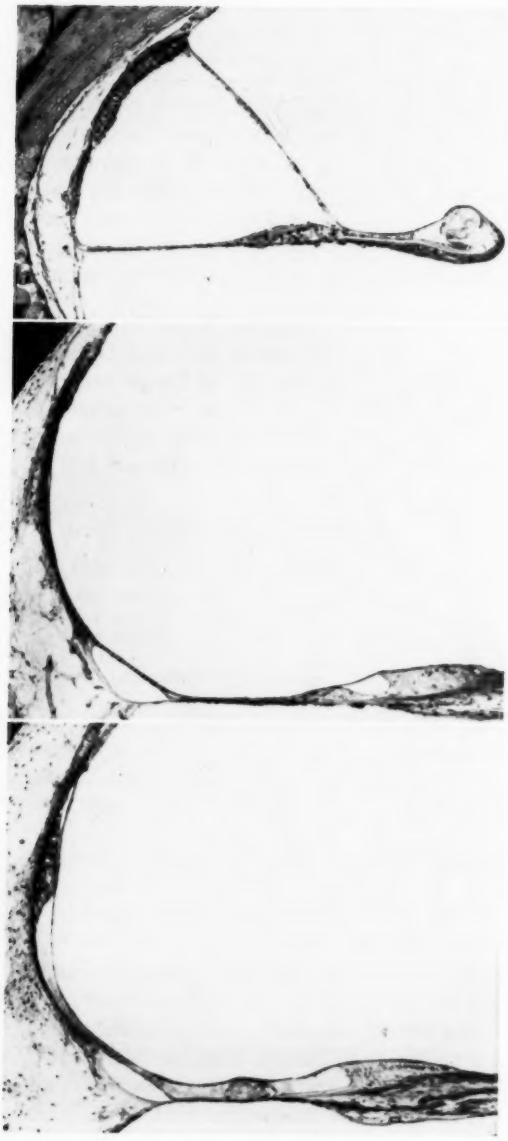
Middle Ear. The epithelium was delicate with no evidence of recent or old inflammatory reaction. The ossicles and tympanic membrane were intact.

Labyrinthine Capsule. The bony capsule appeared normal.

Inner Ear. The membranous structures were fairly well preserved. Moderate postmortem degeneration was present particularly in the vestibular system but the histopathologic changes could be clearly differentiated.

Perilymphatic System. No debris was seen throughout the perilymphatic spaces. An increase in volume of the scala vestibuli was present due to the shift of Reissner's membrane.

Endolymphatic System. Reissner's membrane in the basal and greater portion of the middle coil was collapsed and appeared attached in some areas to the degenerated stria vascularis, spiral prominence, outer and inner sulcus cells and the limbus (Fig. 5). In the distal middle and apical coils Reissner's membrane was in its normal position (Fig. 5A). The depression and attachment of Reissner's membrane



to the structures beneath was interpreted as a true pathologic change because of the presence of an exudate and evidence of reparative fixation in some areas.

Stria Vascularis. The stria vascularis was almost completely degenerated except for remnants in the apical and middle coils.

Tectorial Membrane. In the basal and lower middle coils, detachment of the tectorial membrane from the limbus had taken place and the remnant was present on the basilar membrane as a small amount covered by flattened cells. In the middle coil in some areas it lay rolled up in the angle between Reissner's membrane and limbus, covered by flattened cells. In the upper middle and apical coils it remained attached but was thinned out and depressed into the inner sulcus and onto Corti's organ.

Corti's Organ. There was complete absence of the organ of Corti in the basal and lower middle coils. In the upper middle and apical coils the generation was less but so few hair cells were present that plotting of the organ of Corti was considered of no value (Fig. 6). These changes again paralleled closely the changes in the stria vascularis.

Nerve and Ganglion. The peripheral cochlear neurons and ganglion cells of the apical and middle coils appeared in normal numbers. In the lower part of the basal coil the peripheral cochlear neurons appeared to be diminished. The impression was obtained of slight diminution in numbers of ganglion cells supplying the lower basal coil.

Vestibular System. The saccula and utricle were normal with no collapse or distention. The maculae of both showed some postmortem autolytic changes with areas of granular precipitate formation, agglutination of the otoconia and vacuolization of sensory and supporting cells with pyknotic nuclei. Thoughout the membranous semicircular

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Fig. 5.—Photomicrographs of the cochlear duct in the middle portion of the apical A, middle B and basal coils C of the right ear. Reissner's membrane is depressed obliterating the scala media in the basal C and middle coils B. Degeneration of the stria vascularis is evident in all coils. The tectorial membrane and Corti's organ are shown at higher magnification in Figure 6.

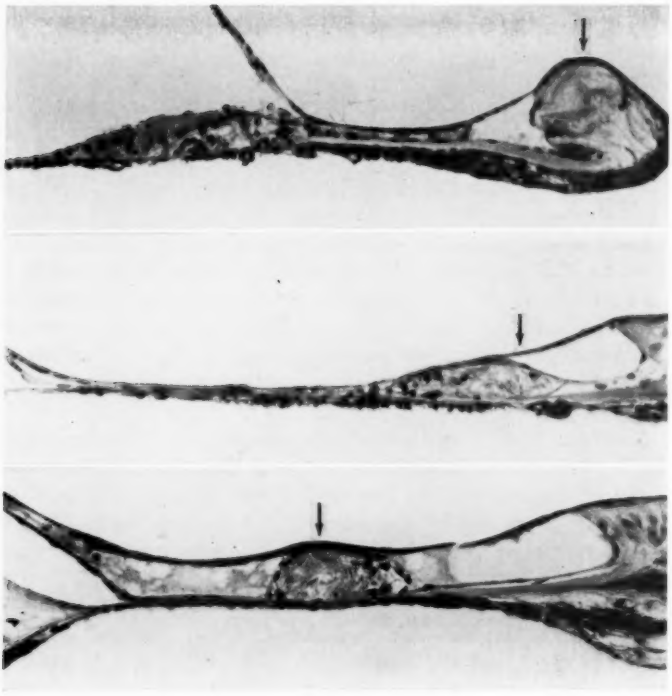

Fig. 6.—Photomicrographs of the apical A (top photo), middle B, and basal coils C of the right ear showing the degenerated tectorial membrane (arrows) and the absence of Corti's organ in the basal and middle coils. In the apical coil the cells in Corti's organ can mostly be identified but the tectorial membrane is no longer in position.

canals there were localized pink staining blebs, within the endothelium. Some areas contained amorphous precipitate. All three of the crista were intact with small cupular remnants attached.

COMMENT

Both inner ears showed marked damage and destruction to the peripheral auditory system with minimal pathological changes in the

vestibular system. The damage was similar on the two sides but more severe on the right. The perilymphatic spaces in both ears were normal except for increased volume of the scala vestibuli of the right ear, secondary to the depressed Reissner's membrane.

The pathological changes of both sides were confined primarily to the cochlear duct. The changes consisted of degeneration and destruction of the stria vascularis, organ of Corti, and tectorial membrane in the basal coil, the degree of degeneration diminishing progressively toward the apex. There was some degeneration of the peripheral cochlear neurons of the lower basal coil but the nerve and ganglion cells of the upper middle and apical coils appeared normal. Hair cell degeneration in the organ of Corti of the left cochlea was plotted (Fig. 4). The severity of destruction of Corti's organ paralleled closely the degenerative changes in the stria vascularis and tectorial membrane as shown in the graph (Fig. 2). In the more severely damaged right ear, Reissner's membrane was collapsed in the basal and lower middle coils and appeared attached to the remnants of stria, inner and outer sulcus cells, organ of Corti, and limbus spiralis. In many areas the outer sulcus cells were stripped up from their base (artifact) and attached to the collapsed Reissner's membrane and in some areas a thin layer of deep pink staining precipitate lay between.

The pathological changes in both inner ears were confined almost entirely within the cochlear endolymphatic system. Certain of the histopathological changes were similar to those seen in inner ear deafness due to the measles virus.[25] However, in the present case the findings represent the end stage of healing whereas in the case of measles[25] there were indications of subacute inflammatory activity. Both the mumps virus and measles virus produce deafness more frequently than vestibular damage.

The diffuse damage to the vascular beds seen in the histological studies of other involved organs and the presence of the highly vascular bed of the stria vascularis may explain the predilection of the cochlea to injury.

If the primary damage to the cochlea occurs by way of the stria vascularis, one can postulate a secondary damage to the tectorial membrane and organ of Corti. This might be a toxic effect or more

likely a non-suppurative inflammatory effect of the virus. The latter was interpreted to be the pathogenesis in the case of measles formerly reported by Lindsay and Hemenway.[25]

The explanation for the complete degeneration in the basal coils with progressively less damage in the upper coils was not apparent from the sections. The preservation of the peripheral cochlear neuron in the presence of subtotal or total degeneration of Corti's organ was a significant finding. This did not correspond to the findings in animal experiments[26] where traumatic damage to the supporting structures was followed by ascending degeneration of the peripheral neuron.

Unilateral deafness like unilateral parotid or testicular involvement probably represents a severe injury to the one organ while the other was bypassed or only subclinically involved. In both the testes and inner ear we are dealing with delicate, highly differentiated tissues. Damage to either is permanent, since regenerative powers are lacking.

The permanent degeneration of the cochlear receptors is in striking contrast to the usually transient paralysis which occurs in the facial, abducens, trigeminal and optic nerves.

The changes in these inner ears are best described as an "endolymphatic labyrinthitis" of viral origin. They were probably ushered in by an inflammatory involvement of the stria vascularis, during the course of a viremia.

The diagnosis of deafness due to mumps is not difficult when associated with clinical parotitis. However, when sudden deafness occurs without parotitis, or in the presence of aseptic meningitis, the diagnosis rests upon laboratory tests. Kilham[27] describes the ease of isolation of the mumps virus and describes success in all 21 attempts to isolate the virus in mumps meningo-encephalitis. The demonstration of the appearance or increase in antibody by compliment fixation test has been described by Enders et al.[28] The diagnosis of infection by a mumps virus using this test rests upon change in antibody titer in two serum specimens, taken at appropriate intervals following the onset of the disease.

The presence and change in the antihemagglutinin titer is a simpler test. This specific factor[29,30] inhibits the agglutination of chicken

or human erythrocytes. These tests and, especially the latter because of its simplicity, are recommended[31] as aids in detection of a mumps infection, clinical or occult. A skin test has been described,[32] but a positive test indicates only that the patient has had an immune response to the mumps virus at some time in the past.

The treatment, as for simple parotitis, is symptomatic. Whole blood, convalescent serum and gamma globulin have been tried without influencing the poor prognosis for return of hearing.

SUMMARY

1. The histopathological changes in the temporal bones of a well documented case of bilateral deafness due to mumps have been presented. No previous description of the histopathology has been found.

2. The degenerative changes consisted of atrophy of the stria vascularis, tectorial membrane and organ of Corti. The degree of atrophy progressed from mild changes in the apical coils to total loss of these structures in the lower middle and basal coils.

3. The pathologic process in the inner ear was confined to the structures within the endolymphatic system of the cochlea, and may be designated best as an endolymphatic labyrinthitis due to the mumps virus.

950 East 59th St.

REFERENCES

1. Hippocrates: Cited by Wesselhoeft, C.: Mumps, in Oxford Loose Leaf Medicine, New York, Oxford University Press, 5:II:489-497 (36).

2. Hamilton, R.: Cited by Wesselhoeft, C.: Mumps, in Oxford Loose Leaf Medicine, New York, Oxford University Press, 5:II:489-497 (36).

3. Johnson, C. D., and Goodpasture, E. W.: An Investigation of the Etiology of Mumps. J. Exper. Med. 59:1, 1934.

4. Kane, L. W., and Enders, J. F.: Immunity in Mumps. III. The Compliment Fixation Test as an Aid in the Diagnosis of Mumps Meningo-encephalitis. J. Exper. Med. 81:137, 1945.

5. Bang, H., and Bang, J.: Involvement of the Central Nervous System in Mumps. Acta Medica Scandinavica 113:487, 1943.

6. Wesselhoeft, C.: Mumps in Oxford Loose Leaf Medicine, New York, Oxford Univ. Press, 5:II:489-497 (36), 1941.

7. Hinze, A.: Cited by Everberg, G.: Deafness Following Mumps. Acta Oto-Laryng. 48:397-403, 1957.

8. Toynbee, J.: Cited by Everberg, G.: Deafness Following Mumps. Acta Oto-Laryng. 48:397-403, 1957.

9. Amarante, R.: Deafness Following Epidemic Parotitis. Arch. Oto-laryng. 63:8, 1956.

10. Eley, R. C.: Neurologic Conditions in Infants and Children. J. Pediat. 7: 248, 1935.

11. Thiebaut, F., Greiner, G. F., Isch, F., Mazoue, F.: Surdite unilaterale meningite ourlienne. Rev. Oto-neuro-opht. Par. 26:(4):251, 1954.

12. Fuhrmann, K. H.: Neurocomplications in Epidemic Parotitis. Latent Parotitic Meningitis. Acta Psych. et Neuro. 8:1, 1938.

13. Kjaer, M.: On the Relation Between Parotigenous Meningitis and Acusticus Neuritis. Acta Otolaryng. 33:55, 1944.

14. Boat, G. W.: Non-suppurative Involvement of the Labyrinth in the Course of Mumps. Report of 2 Cases. J.A.M.A. 51:1961, 1908.

15. Hubbard, T.: Nerve Deafness and Mumps. Tr. Am. Otol. Soc. 13:451, 1951.

16. McKaig, C. B., and Woltman, H. W.: Neurologic Complications of Epidemic Parotitis. Report of a Case of Parotitic Myelitis. Arch. Neurol. and Psychiat. 13: 451, 1915.

17. Lindsay, J. R.: Sudden Deafness Due to Virus Infection. Arch. Otolaryng. 69:13-18, 1959.

18. Johnson, C. D., and Goodpasture, E. W.:The Histopathology of Experimental Mumps in the Monkey, Macacus rhesus. Am. J. Path. 12:495, 1936.

19. Smith, G. G.: Cited by Wesselhoef, C.: Mumps, in Oxford Loose Leaf Medicine, New York, Oxford Univ. Press, 5:II:489-497 (36), 1941.

20. Gall, E. A.: The Histopathology of Acute Mumps Orchitis. Am. J. Path. 23:637-651, 1947.

21. Everberg, G.: Deafness Following Mumps. Acta Oto-laryng. 48:397-403, 1957.

22. Bordley, J. E., Hardy, W.: The Etiology of Deafness in Young Children. Acta Oto-laryng. 40:72-79, 1951.

23. Guild, S. R.: A Graphic Reconstruction Method for Study of the Organ of Corti. Anat. Rec. 22:141-147, 1921.

24. Schuknecht, H. F.: Techniques for Study of Cochlear Function and Pathology in Experimental Animals. Arch. Otolaryng. 58:377-397, 1953.

25. Lindsay, J. R., and Hemenway, W. G.: Inner Ear Pathology Due to Measles. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 63:754, 1954.

26. Sutton, S., and Schuknecht, H.: Regional Hearing Losses from Induced Cochlear Injuries in Experimental Animals. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 63:727, 1954.

27. Kilham, L.: Mumps Meningo-encephalitis With and Without Parotitis. Am. J. Dis. Child. 78:324, 1949.

28. Enders, J. F., Kane, L. W., Cohen, S., and Levens, J. H.: Immunity in Mumps. I. Experiments with Monkeys. The Development of Compliment Fixing Antibody Following Infection and Experiments on Immunization by Means of Inactivated Virus and Convalescent Human Serum. J. Exp. Med. 81:93, 1945.

29. Levens, J. H., and Enders, J. F.: The Hemo-agglutinative Properties of Amniotic Fluid from Embryonated Eggs Infected with Mumps Virus. Science 102: 117, 1945.

30. Robbins, F. C., Kilham, L., Levens, J. H., and Enders, J. F.: An Evaluation of the Test for Antihemagglutinens in the Diagnosis of Infections by the Mumps Virus. J. Immunol. 61:235, 1949.

31. Enders, J. F.: Mumps, in Rivers, T. M., Jr.: Viral and Rickettsial Infections of Man. 2nd ed., Philadelphia, J. B. Lippincott Co., pp. 513-521, 1952.

32. Enders, J. F.: Observations on Immunity in Mumps. Ann. Int. Med. 18:6: 1015, 1943.

LXVIII

THE ACTION OF ENZYMES ON HUMAN MIDDLE EAR EFFUSIONS

CARL F. GESSERT, PH.D.

ELIZABETH S. BAUMANN, B.A.

BEN H. SENTURIA, M.D.

ST. LOUIS, MO.

This is one of a series of reports on studies dealing with the pathogenesis and treatment of tubotympanitis. Microscopic examinations, bacteriological studies and chemical analyses have previously been reported for specimens of human middle ear effusions which were collected by aspiration of the tympanic cavity.[1,2] The experimental production of effusions in dogs and the resultant microscopic and chemical findings were published recently.[3,4]

Our results in these first studies suggested that certain chemical constituents with large, complex molecules contributed to the high viscosity of the effusions and made their removal from the middle ear extremely difficult. Thus it seemed desirable to investigate the possibility that these molecules might be broken down by the action of available enzymes and in this manner facilitate drainage or absorption of the effusion.

This report is concerned primarily with *in vitro* studies of the action of certain enzymes on human middle ear effusions and some preliminary *in vivo* observations.

From the Department of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri.

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REVIEW OF PREVIOUS INVESTIGATIONS

In the course of reviewing the literature for our earlier investigations it became evident that some specific and understandable classification of middle ear effusions was necessary. On the basis of microscopic findings,[1] three main categories of effusions were established (Table I).

TABLE I

CLASSIFICATION AND CHARACTERISTICS OF MIDDLE EAR EFFUSIONS

CATEGORY OF THE EFFUSIONS	MICROSCOPIC CHARACTERISTICS			PHYSICAL APPEARANCE
	NEUTROPHILES	CELLULAR REMNANTS	MUCUS-LIKE STRANDS	
Serous	Rare	Rare	None	Amber, clear, low viscosity
Purulent	Numerous	Moderate	Rare	Gray to white, turbid, medium viscosity
Mucopurulent	Few	Numerous	Numerous	Gray, translucent, rubbery, high viscosity

Serous effusions were amber colored and translucent, low in viscosity and easily removed from the ear. They contained essentially no cells or cellular material, but occasionally a neutrophile, lymphocyte, large phagocyte or cellular remnant was found.

Purulent effusions were characteristic of classical suppurative otitis media. They were turbid, gray to white in color and slightly more viscous than the serous type. These effusions contained myriads of intact neutrophiles and a moderate number of mucus-like strands and cellular remnants.

The *mucopurulent* effusions were gray to tan, translucent, highly viscous and rubbery. These specimens were difficult to aspirate from the middle ear and awkward to handle during analyses because of their thick, tenacious properties. They contained numerous mucus-like strands, many cells in various stages of degeneration and a few intact neutrophiles. (A fourth kind of effusion termed *mucoid* was also found occasionally; it differed from the mucopurulent in that it

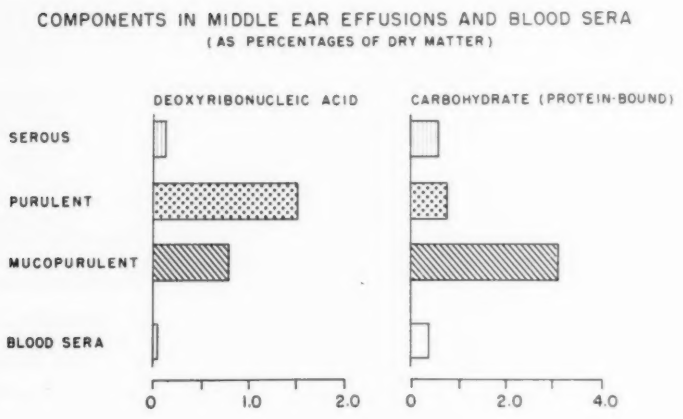

Figure 1

contained almost no cells or cellular remnants, but did contain numerous mucus-like strands.)

Certain analyses were made of effusions in each of the categories in order to determine any differences in their chemical properties which might account for the striking dissimilarities in their physical properties.[1] Furthermore, a knowledge of some of the chemical properties of the specimens might suggest methods for eliminating these effusions from the middle ear.

Among the constituents which were measured, deoxyribonucleic acid (DNA) and protein-bound carbohydrate were considered most likely to be responsible for the high viscosity, since both of them can participate in the formation of polymers or large complex molecules. DNA, a main constituent of nucleoprotein, is found primarily in cell nuclei, so it was not surprising that purulent effusions, which contain many neutrophiles, were highest in DNA content (Fig. 1). Mucopurulent effusions, with their high content of cellular remnants and some neutrophiles, also contained much more DNA than serous effusions.

The analyses also showed that mucopurulent effusions were especially rich in carbohydrate bound to protein. Purulent specimens contained slightly more of this type of carbohydrate than serous effusions, but considerably less than the mucopurulent. Since mucopurulent effusions are much more viscous than purulent, it appears that the protein-bound carbohydrate probably contributes more to the viscosity of middle ear effusions than does DNA.

The exact nature of the carbohydrate-protein complex present in the effusions has not been determined. The combination of carbohydrate with protein can be either mucoprotein or glycoprotein. Mucoprotein is defined as a complex of protein and mucopolysaccharide held together by a polar or other easily split bond, while glycoprotein is a substance which has primarily the properties of proteins, but contains appreciable amounts of carbohydrate (0.5% or more hexosamine) firmly bound to the protein, probably covalently.[5]

The method by which protein-bound carbohydrates in ear effusions were determined in our studies[1] was presumed to measure glycoprotein. The carbohydrate entity must have been firmly bound to the protein since it was precipitated with the protein in a cold perchloric acid solution and required heating at 90° C. in order to hydrolyze and separate it from the protein. Since the carbohydrate units in such a complex are likely not linked together in the form of a polysaccharide, but rather are dispersed throughout the molecule,[5,6] it seemed that an attack with proteolytic enzymes on the peptide linkages within the protein might be a good way to break up the complex and thereby reduce viscosity.

However, since DNA might also contribute to the high viscosity, especially in the mucopurulent specimens in which cells are partially disintegrated, the action of deoxyribonucleases (dornases) was also tested.

Both proteolytic enzymes and dornases have been used *in vitro* to break down various components of exudates. Trypsin and chymotrypsin demonstrated good mucolytic action on mucus, sputum and other secretions, greatly reducing viscosity.[7-10] Streptodornase was found to decrease considerably the viscosity of purulent exudates.[11,12]

IN VITRO ACTION

Experimental Procedure. In vitro studies were performed by treating samples of various effusion specimens with solutions of commercial enzymes. Each enzyme was tested in various concentrations either in a buffered solution at or near its pH of optimum activity, or in physiologic saline. Most of the activity was measured using enzyme solutions of 4 mg/ml which were mixed with an equal volume of effusion specimen and incubated at room temperature or in a water bath at 38° C.

After given intervals, all enzyme action in a measured portion of the incubation mixture was stopped by the addition of an equal volume of 12% perchloric acid (PCA), which precipitates the whole protein. The hydrolyzed protein, which is not precipitated but remains in the PCA supernatant, was measured.[13] This procedure for determining proteolytic activity is essentially similar to that of Anson.[14]

DNA is ordinarily precipitated along with whole protein by cold PCA. When an effusion was treated with a dornase, any DNA that became depolymerized was no longer precipitated by PCA. The amount of depolymerized DNA soluble in the PCA supernatant solution could then be determined by a fluorometric method,[15] as a measure of dornase activity.

Besides these quantitative methods to measure enzyme action, qualitative criteria were also used. Gross changes in physical appearance were noted, an increase in fluidity after treatment indicating lysing action of the enzyme. In later studies, smears were made of the specimens before and after enzyme treatment to determine any changes which might be revealed by microscopic examination.

The enzymes tested included proteolytic enzymes (trypsin,* chymotrypsin, pepsin and papain), dornases of both pancreatic* and bacterial† origin, hyaluronidase and lysozyme, which are known to act on certain polysaccharides, and human plasmin‡ (fibrinolysin).

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*Tryptar (Armour Pharmaceutical) for topical use and Parenzyme (National Drug) for intramuscular use.

* Dornavac (Merck Sharp & Dohme)

† Varidase (Lederle), streptodornase together with streptokinase.

‡ Merck Sharp & Dohme.

TABLE II

ACTIONS OF ENZYMES ON MIDDLE EAR EFFUSIONS *IN VITRO*

ENZYMES	GROSS OBSERVATIONS: LYSING ACTION (Decreased Viscosity)	CHEMICAL MEASUREMENT: PROTEIN HYDROLYZED	CHEMICAL MEASUREMENT: DNA DEPOLYMERIZED
Proteolytic:			
Trypsin	+++	+++	0
Chymotrypsin	+++	+++	0
Pepsin	+++	+++	
Papain	+++	+++	
Deoxyribonucleases:			
Bacterial	+	0	+++
Pancreatic	+	0	+++
Other:			
Plasmin (Fibrinolysin)	0	0	0
Lysozyme	0	0	
Hyaluronidase	0	0	

For reasons explained later, most of the *in vitro* studies were made with trypsin, chymotrypsin and pancreatic dornase. Usually the action of one of the proteolytic enzymes was compared with that of the dornase for their relative abilities to cause viscous effusions to become fluid. In some instances, the chemical analyses were made for evidence of both proteolytic and dornase activity, no matter which type of enzyme was used. In this way the protease and the dornase served in effect as controls for each other; that is, measurements were made to determine whether any protein was hydrolyzed by the dornase and whether any DNA was depolymerized by the protease.

Several combinations of trypsins and dornases were tested for supplementary or potentiating effects which they might have on each other. Two trypsin preparations were each used in combination with the pancreatic and also with the bacterial dornase. The four enzymes were used individually as well on the same specimens. They were prepared in 0.1 M phosphate buffer, pH 7.0, with the addition of calcium or magnesium ions. The final concentration of each enzyme

TABLE III

IN VITRO ACTION OF ENZYMES ON COMPONENTS OF MUCOPURULENT EFFUSIONS

ENZYME USED*	PROTEIN HYDROLYZED†	DNA DEPOLYMERIZED†
Buffer only	1.13 ± 1.03	.019 ± .010
Trypsin	6.42 ± 2.04	.035 ± .027
Pancreatic dornase	1.65 ± 1.08	.351 ± .168

* Enzyme concentration, 4 mg/ml in buffer; incubated at 38° C. overnight.

† Averages for six specimens as mg/ml PCA supernatant ± S. D.

after addition to the specimen was the same (2 mg/ml), whether that enzyme was present alone or in combination with another.

Findings. In general, it was found that the proteolytic enzymes were very effective in causing the viscous specimens to become fluid, whereas all other enzymes tested were not (Table II). Human plasmin did not lyse the viscous effusions, nor did it hydrolyze the protein to any great extent. Neither lysozyme nor hyaluronidase showed any lysing activity on mucopurulent effusions, so these two enzymes were not examined further.

Dornase* caused the DNA to become depolymerized but it did not bring about any striking lysis of the effusions. In spite of the failure of deoxyribonuclease to reduce viscosity appreciably, the investigation of its action was continued because of the effectiveness shown in breaking down DNA in these effusions, and reports of the clinical usefulness of dornases.[11,12,16-18] Although each of the proteolytic enzymes was capable of accomplishing the desired reduction in viscosity, trypsin† and chymotrypsin were selected for more detailed studies since they have had more extensive clinical applications.[8,19,20]

* Pancreatic dornase was used more extensively than bacterial (streptococcal) dornase. The difference between them did not appear to be of any significance for *in vitro* studies.

† There was no *in vitro* difference apparent between trypsins intended for intramuscular and for topical use.

TABLE IV

IN VITRO ACTION OF ENZYMES ON COMPONENTS OF PURULENT EFFUSIONS

ENZYME USED*	PROTEIN HYDROLYZED†	DNA DEPOLYMERIZED†
Buffer only	1.07	.017
Trypsin	6.00	.022
Pancreatic dornase	1.39	.478

* Enzyme concentration, 4 mg/ml in buffer; incubated at 38° C. for 2 hours, then overnight at room temperature.

† Averages for two specimens as mg/ml PCA supernatant.

TABLE V

SEROUS EFFUSION PROTEIN HYDROLYZED BY ENZYMES *IN VITRO*

ENZYME USED*	PROTEIN HYDROLYZED†
Saline only	0.47
Trypsin	7.37
Chymotrypsin	7.62

* Enzyme concentration, 4 mg/ml in 0.85% saline; incubated at 38° C. for 90 minutes.

† Averages for four specimens as mg/ml PCA supernatant.

In Table III a typical comparison is shown between the chemical actions of trypsin and pancreatic dornase on mucopurulent effusions. As expected, the trypsin hydrolyzed protein, but had little effect in depolymerizing DNA, while the dornase had minimal effect in hydrolyzing protein, but did depolymerize DNA. Proteolytic enzyme activity was always accompanied by the physical finding of an increased fluidity of the effusion, while dornase action was associated with less perceptible or no change in viscosity.

TABLE VI

HYDROLYSIS OF PROTEIN* BY ENZYMES INDIVIDUALLY AND IN COMBINATION

SPECIMEN	BUFFER ONLY	TRYPSINS†		DORNASES‡		COMBINATIONS			
		P	T	D	V	P&D	P&V	T&D	T&V
Mucopurulent A	0.7	6.3	7.1	1.1	0.9	7.7	6.0	7.8	6.6
Mucopurulent B	0.7	1.9	2.6	1.0	0.7	5.9	1.7	6.5	
Mucopurulent C	1.0	6.0				8.1	5.8		
Purulent D	1.0	5.5	6.4	-1.5	1.1	6.3	5.5		
Casein & DNA§	0.4	2.3	2.7	1.9	1.5	2.6	2.5	2.9	2.9

* Hydrolyzed protein expressed as mg/ml PCA supernatant.

† P = Parenzyme; T = Tryptar.

‡ D = Dornavac; V = Varidase (streptodornase and streptokinase).

§ A control solution containing 0.8% casein and 0.04% DNA.

Although the action of these enzymes on viscous, mucopurulent effusions was of the most interest, their activity on purulent and serous specimens was also investigated. The proteolytic enzymes were found to hydrolyze protein in both purulent and serous specimens (Tables IV and V). Dornase depolymerized the DNA in purulent effusions but it was not tested on serous effusions as they contain practically no cells or DNA. Since most of the purulent or serous specimens were not very viscous even before treatment, the enzyme activity did not result in readily perceptible changes in fluidity.

The data in Tables VI and VII show what happened to individual specimens which were treated with trypsins and dornases singly and in combination. It appears that the proteolytic activity (Table VI) was somewhat greater when the pancreatic dornase was present with intramuscular trypsin than when the trypsin was acting alone. Bacterial dornase did not increase the hydrolysis of protein by either trypsin preparation. The proteolytic activity obtained with the topical trypsin was not substantially increased by the presence of pancreatic dornase, with one exception: in mucopurulent specimen *B* the proteolytic activity of both trypsin solutions was increased two to three-fold when the pancreatic dornase was added. When dornase activity is

TABLE VII

DEPOLYMERIZATION OF DNA* BY ENZYMES INDIVIDUALLY AND IN COMBINATION

SPECIMEN	BUFFER ONLY	TRYPSINS†		DORNASES‡		COMBINATIONS			
		P	T	D	V	P&D	P&V	T&D	T&V
Mucopurulent A	.021	.088	.061	.547	.514	.631	.561	.655	.471
Mucopurulent B	.013	.023	.019	.156	.132	.141	.142	.175	
Mucopurulent C	.025	.052				.284	.200		
Purulent D	.020	.031	.024	.343	.274	.345	.256		
Casein & DNA§	.002	.004	.005	.135	.106	.148	.118	.104	.113

* Depolymerized DNA expressed as mg/ml PCA supernatant.

†) ‡) See corresponding footnotes of Table VI.

§)

considered (Table VII), it appears that the trypsins usually did not enhance the action of either dornase, except in mucopurulent specimen *A*. (A direct comparison between the actions of pancreatic and bacterial dornases as shown in Table VII is not justified in this instance. Although their solutions were prepared in equal concentrations by weight, their dornase activities on purified DNA solutions were not quite equivalent.)

Microscopic observations made on smears of mucopurulent effusions indicated that the mucus-like strands always disappeared after treatment with proteolytic enzymes and in some instances after dornase action. It seemed that whenever a substantial reduction in viscosity occurred after enzyme action, the strands were completely gone.

For possible *in vivo* application, it was of interest to know what enzyme concentration is required to obtain good *in vitro* proteolytic activity, so a wide range of enzyme concentration was tested on two effusions (Table VIII). On specimen *E*, satisfactory activity was obtained in one-half hour at concentrations of 10 and 1 mg/ml, but no activity was apparent at 0.1 mg/ml and less. A similar test on specimen *F* showed that even a concentration of 1 mg/ml was ineffective in this instance, while 10 mg/ml was effective.

TABLE VIII

IN VITRO HYDROLYSIS OF PROTEIN* IN PURULENT EFFUSIONS BY VARIOUS CONCENTRATIONS OF TRYPSIN AND CHYMOTRYPSIN

SPECIMEN	ENZYME CONCENTRATION	TRYPSIN		CHYMOTRYPSIN	
		INCUBATION TIME (MINUTES)			
	mg/ml	0	30	0	30
E	0	.50	.58	.49	.52
	0.001	.49	.55	.49	.55
	0.01	.43	.47	.45	.52
	0.10	.47	.54	.50	.53
	1.0	.74	2.25	.61	2.33
	10.0	1.47	6.31	1.25	6.01
F	0	1.12	1.13	1.09	1.30
	0.10	1.10	1.32	1.08	1.05
	0.50	1.18	1.30	1.20	1.04
	1.0	1.36	1.45	1.27	1.13
	10.0	2.08	4.75	2.08	4.41

* Hydrolyzed protein expressed as mg/ml PCA supernatant.

It was necessary to store many of the effusion specimens in a deep frozen state until they could be analyzed. In order to ascertain that the freezing, storage and thawing of the specimens did not either denature the substrate protein and thus make it less resistant to proteolysis,[21] or inactivate proteolytic enzyme inhibitors which might be present in the effusions,[22] tests were made on several fresh mucopurulent specimens shortly after they were obtained from patients. The data in Table IX show that a considerable amount of protein hydrolysis by trypsin and chymotrypsin had occurred in thirty minutes. In ninety minutes the protease activity on the fresh specimens was comparable to that on frozen specimens in the same or a longer period of time (Tables III, V).

IN VIVO STUDIES

Chymotrypsin* was given in recommended dosage for buccal absorption to six patients with middle ear effusions without improve-

* Chymar Buccal (Armour Pharmaceutical), 10,000 Armour proteolytic units per tablet.

TABLE IX

PROTEIN HYDROLYZED* BY ENZYMES *IN VITRO* IN "FRESH" MUCOPURULENT EFFUSIONS

	SALINE ONLY			TRYPSIN†		CHYMOTRYPSIN†	
	INCUBATION TIME (MINUTES)						
SPECIMEN	0	30	90	30	90	30	90
G	.54	.57	.55	3.97	6.27		
H	.68	.64	.67	3.34	5.23		
J	.75	.63	.54			3.59	5.60
K	.73	.57	.53			4.32	6.16

* Hydrolyzed protein expressed as mg/ml PCA supernatant.

† Enzyme concentration, 4 mg/ml in 0.85% saline.

ment of clinical findings. Two of the patients developed severe ulceration and erythema of the buccal mucous membrane.

After otologic and audiologic examinations, ten patients were each given one tablet of enteric coated chymotrypsin* three times daily for five to seven days, and then the examinations were repeated. Four patients showed improvement of symptoms, but in only one instance did the effusion disappear. In the remaining cases no clinical evidence of improvement in the diseased condition was observed.

In five of these patients myringotomy was performed (three bilaterally) after the oral chymotrypsin therapy, and fluid was aspirated from the eight ears. Characteristics of the mucopurulent category were revealed on microscopic examinations, yet the viscosity of five specimens seemed to be less than usual for effusions of that category. However, the concentrations of total protein found in these same five (Table X) were within the normal range for mucopurulent specimens,[1] and the amounts of hydrolyzed protein were comparable to those found in the untreated control specimens in our *in vitro* enzyme studies. (See Table III. For comparison with Table X, 1.0 mg/ml in PCA supernatant is equivalent to 0.20% of the whole speci-

* Chymoral (Armour Pharmaceutical), 50,000 Armour proteolytic units per tablet.

TABLE X

TOTAL AND HYDROLYZED PROTEIN IN EFFUSIONS FROM PATIENTS TREATED WITH CHYMOTRYPSIN GIVEN ORALLY

SPECIMEN	AS PER CENT OF WHOLE SPECIMEN	
	TOTAL PROTEIN	HYDROLYZED PROTEIN
L	12.4	0.19
M	14.4	0.18
N	14.7	0.23
P	11.8	0.22
Q	8.6	0.21

men.) These data indicate that there was no chemical evidence that whole protein had decreased or that hydrolysis of the effusion had occurred within the tympanic cavity following the oral administration of enteric coated chymotrypsin.

COMMENT

One of the primary purposes of testing the *in vitro* action of various enzymes on middle ear effusions was to find a way to reduce the viscosity of the thick, tenacious rubbery specimens. The proteolytic enzymes hydrolyzed the protein in all types of effusions, and by no means acted exclusively on carbohydrate-protein complexes. However, it is believed that it was only when there was a substantial amount of such a complex present that the viscosity was high enough to show a striking reduction by protease activity. A disappearance of the strands observed in smears of mucopurulent effusions, at least part of which are believed to be composed of carbohydrate-protein complex, appeared to accompany proteolytic activity and a reduction in viscosity.

Striking reductions in viscosity of purulent pleural exudates by streptodornase *in vitro* and *in vivo* have been described.[12] In most of our middle ear effusions on which dornases were tested, no great change in viscosity was readily apparent. This finding was interpreted

to mean that some component other than DNA was primarily responsible for the highly viscid characteristics. Furthermore, mucopurulent effusions are more viscous than purulent specimens, even though the latter contain more DNA.

Neither plasmin itself nor the streptokinase (plasminogen activator) which was present with the streptodornase that was tested had any obvious effect on the physical properties of the mucopurulent effusions. These findings would suggest that fibrin was not a significant factor in the high viscosity of the effusions.

Inhibitors of trypsin are known to be present in blood plasma and soft tissues.[22] It is likely that they are also present in the effusions in various amounts, since higher concentrations of the enzyme are required for some specimens than others in order to exert comparable proteolytic action. The approximate range of enzyme required appears to lie between 1 and 10 mg/ml of solution added to an equal volume of effusion. On purified substrates where no inhibitors are present, trypsin and chymotrypsin will show protease activity at about 0.01 mg/ml (1:100,000).[23]

When two trypsin preparations were each tested in combination with pancreatic and bacterial dornases, the enzymes did not generally appear to enhance or inhibit one another. In one specimen, however, the proteolytic activities of both trypsin preparations were greatly increased by the presence of pancreatic dornase. It is speculated that some trypsin inhibitor present in this particular specimen was modified or destroyed by the dornase, thus allowing the trypsin to exert its full protease potential. Further investigation of this possibility is needed for a better understanding of this effect.

In view of results obtained by others, one is led to believe that a combination of a proteolytic enzyme and a dornase might be more effective in reducing viscosity and breaking down the cell remnants present in the mucopurulent category. Even though our studies showed, with one exception, no augmentation by this combination of enzymes *in vitro,* the desirability of testing these combinations *in vivo* is not ruled out.

In general, two principal ways are available for bringing the enzymes into contact with the diseased locus, i.e., either the enzyme must

be transported by the blood stream from the point of administration to the site of action, or the enzyme may be applied directly into the area where the substrate is located. There are a number of problems which should be considered before any particular route of enzyme administration is chosen for the treatment of middle ear effusions.

Some difficulties have been encountered in the parenteral use of proteolytic enzymes. Intravenous injections caused hemorrhagic pathologic changes;[24] this route is therefore not recommended. Trypsin in oil given intramuscularly is known to cause severe local pain, but more purified preparations in an aqueous medium are said to have minimized the local intramuscular reactions. A severe shock syndrome and generalized urticaria have been reported in animals and occasionally in humans after parenteral administration of chymotrypsin.[24-27] Defective wound healing and subconjunctival blebs occurred after the local use of chymotrypsin in the eye.[28]

Investigation with rabbits[29] raised some doubt that trypsin and chymotrypsin given intramuscularly could increase the proteolytic activity in blood. However, it was later suggested that sufficient time for absorption had not been allowed before the measurements were made.[30] Even if these enzymes do not produce increased proteolytic action at the site of disease when given intramuscularly, it is postulated by some that they may still exert an anti-inflammatory effect. Since inflammation may play a major role in many middle ear effusions,[1] the possible beneficial effects of an anti-inflammatory agent should not be disregarded.

Intramuscular trypsin has been used by Auslander, along with myringotomy and politzerization of the eustachian tube, in the treatment of patients with serous otitis media.[31] A large majority of his patients (89 of 106) required only one myringotomy to effect a cure, whereas previous patients who received no trypsin had had two or more myringotomies performed to obtain comparable results. The absence of suitable controls, however, makes it difficult to evaluate critically the efficacy of this use of trypsin.

There is also some question whether an enzyme given systemically will actually reach its substrate located in a middle ear effusion which is, in a sense, external to the tissues. A similar question was raised when intravenous plus intramuscular injections of pancreatic

dornase were used for the therapy of lung abscesses.[32] A significant increase in dornase activity and a decrease in DNA present in the sputum of treated patients was reported and interpreted as evidence that the enzyme did reach its substrate via the systemic route. Despite the depolymerization of DNA by pancreatic dornase, the viscosity of the sputum actually showed an increase in most cases which was "attributed to the relative increase in the amount of mucus in the sputum." Our *in vitro* observations are in agreement with these *in vivo* findings with regard to the relative ineffectiveness of dornase in reducing the viscosity of an effusion which contains a relatively high amount of mucosubstances.

The buccal administration of chymotrypsin has been suggested recently as a more convenient method than intramuscular or intravenous injection. However, in our experience the occurrence of local reactions with this route has discouraged its use.

Preliminary trials were made with enteric coated tablets of chymotypsin. Some clinical improvement was observed and no adverse reactions occurred, but our observations were too limited to draw any objective conclusions regarding a beneficial effect. The chemical analyses on five specimens aspirated after enzyme treatment gave no evidence of proteolytic action having taken place within the tympanic cavity.

Direct instillation into the middle ear should assure good contact between an enzyme and the effusion which contains its substrate. However, certain precautions must be kept in mind regarding the use of proteolytic enzymes in such a vulnerable area. Further investigative work must be performed to establish that no damage will occur as a result of corrosive action upon the oval and round windows, or by absorption of the enzyme through the round window. Such action might lead to damage of the finer structures of the inner ear, comparable to that which occurred in the retina as reported by the ophthalmologists.[33] The higher the concentration of enzyme used, the greater will be the potential danger.

Two ways in which an enzyme might be instilled into the middle ear can be considered. One such method would be to inject it in proper dilution at the time of myringotomy under general anesthesia, and then remove it after a short interval by aspiration and irrigation

with saline or a neutralizing solution. *In vitro* studies indicate that a concentration on the order of 1 mg/ml (1:1,000 dilution) or more would be required if significant proteolytic activity were to be expected within a short time. At this concentration it is considered necessary that an effective neutralizing agent be used. Another possibility is the insertion of an indwelling polyethylene catheter through the tympanic membrane so that instillation, and neutralization and aspiration could be performed at regular intervals over a period of days or weeks. In this way somewhat lesser concentrations of the enzymes, perhaps on the order of 0.1 mg/ml (1:10,000) might be safe yet effective.

We are aware that improvement occurs in hearing and in the clinical appearance of the tympanic membrane and the middle ear after the insertion of a catheter through the drum. However, we have found that in the mucopurulent category the effusion often recurs shortly after removal of the catheter. By the local use of an enzyme, we hope that proteolytic and possible anti-inflammatory activity will assist in eliminating the underlying factors which cause the effusion.

As we obtain a better understanding of the action of various enzymes on inflammations of the eustachian tube and middle ear, it may be possible to anticipate the sequelae of tubotympanitis. By application of the proper enzymes it should be possible to correct the chemical imbalances between the blood, lymph and interstitial fluids. When this complex interplay of chemical and pathological forces is better understood, one may be able to apply specific and concise measures for the control of effusions which appear in the middle ear.

SUMMARY

In vitro studies were made of the actions of proteolytic enzymes, deoxyribonucleases, lysozyme, hyaluronidase and plasmin on effusions aspirated from middle ears. These investigations revealed that proteolytic enzymes are by far the most efficient of those tested in causing the desired decrease in viscosity, presumably by a partial hydrolysis of the protein.

Deoxyribonucleases acted upon the effusions to depolymerize the DNA, but these enzymes and all others except the proteolytic were

not effective in changing the physical properties of the effusions to any substantial degree.

The administration of enteric coated oral chymotrypsin to six patients with middle ear effusions provided preliminary clinical impressions which suggested that limited improvement may occur in some patients following the use of this form of protease. However, the chemical analysis of five effusion specimens did not yield any data which indicated that the enzyme exerts proteolytic activity on the effusions. More extensive and controlled studies in humans and experimental animals are required before any conclusions can be drawn regarding the efficacy of the use of enzymes for the treatment of middle ear effusions.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

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REFERENCES

1. Senturia, B. H., Gessert, C. F., Carr, C. D., and Baumann, E. S.: Studies Concerned with Tubotympanitis. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 67:440:467, 1958.

2. Senturia, B. H., Gessert, C. F., Carr, C. D., and Baumann, E. S.: Middle Ear Effusions: Causes and Treatment. Tr. Amer. Acad. Ophth. 64:60-72, 1960.

3. Sade, J., Carr, C. D., and Senturia, B. H.: Middle Ear Effusions Produced Experimentally in Dogs. I. Microscopic and Bacteriologic Findings. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 68:1017-1027, 1959.

4. Gessert, C. F., Baumann, E. S., and Senturia, B. H.: Middle Ear Effusions Produced Experimentally in Dogs. II. Some Biochemical and Electrophoretic Properties. ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 68:1028-1036, 1959.

5. Winzler, R. J.: Glycoproteins in Plasma. Ciba Foundation Symposium on Chemistry and Biology of Mucopolysaccharides. Boston, Little, Brown and Company, 1958, pp. 245-267.

6. Bollet, A. J.: Plasma Glycoproteins, Mucoproteins and Mucopolysaccharides. Arch. Int. Med. 104:152-160, 1959.

7. Werner, I.: Studies on Glycoproteins from Mucous Epithelium and Epithelial Secretions. Acta Soc. Med. Upsal. 58:1-55, 1953.

8. Limber, C. R., Reiser, H. G., Roettig, L. C., and Curtis, G. M.: Enzymatic Lysis of Respiratory Secretions by Aerosol Trypsin. J.A.M.A. 149:816-821, 1952.

9. Farber, S. M., Pharr, S. L., Wood, D. A., and Gorman, R. D.: The Mucolytic and Digestive Action of Trypsin in the Preparation of Sputum for Cytologic Study. Science 117:687-690, 1953.

10. Umiker, W., Young, L., and Waite, B.: The Use of Chymotrypsin for the Concentration of Sputum in the Cytologic Diagnosis of Lung Cancer. Univ. Mich. Med. Bull. 24:265-267, 1958.

11. Tillett, W. S., and Sherry, S.: The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous, Purulent and Sanguinous Pleural Exudations. J. Clin. Invest. 28:173-190, 1949.

12. Sherry, S., Johnson, A., and Tillett, W. S.: The Action of Streptococcal Desoxribose Nuclease (Streptodornase) *in vitro* and on Purulent Pleural Exudations of Patients. J. Clin. Invest. 28:1094-1104, 1949.

13. Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J.: Protein Measurement with Folin Phenol Reagent. J. Biol. Chem. 193:265-275, 1951.

14. Anson, M. L.: Estimation of Pepsin, Trypsin, Papain and Cathepsin with Hemoglobin. J. Gen. Physiol. 22:79-89, 1938.

15. Kissane, J. M., and Robins, E.: The Fluorometric Measurement of Deoxyribonucleic Acid in Animal Tissues with Special Reference to the Central Nervous System. J. Biol. Chem. 233:184-188, 1958.

16. Tillett, W. S., Sherry, S., and Christensen, L. R.: Streptococcal Desoxyribonuclease - Significance in Lysis of Purulent Exudate and Production by Strains of Hemolytic Streptococci. Proc. Soc. Exp. Biol. Med. 68:184-188, 1948.

17. Tillett, W. S., Sherry, S., Christensen, L. R., Johnson, A. J., and Hazlehurst, F.: Streptococcal Enzymatic Debridement. Ann. Surg. 131:12-22, 1950.

18. Tillett, W. S., Sherry, S., and Read, C. T.: The Use of Streptokinase-Streptodornase in the Treatment of Chronic Empyema. J. Thoracic Surg. 21:325-341, 1951.

19. Martin, G. J. (ed): Proteolytic Enzymes and Their Clinical Application. Ann. N. Y. Acad. Sci. 68:1-244, 1957.

20. Tanyol, H., Swain, W. M., and Beiler, J. M.: Parenteral Use of Enzymes in Medicine. *In*: G. J. Martin: Clinical Enzymology. Boston, Little, Brown and Company, 1958, pp. 109-143.

21. Haurowitz, F., Tunca, M., Schwerin, P., and Göksu, V.: The Action of Trypsin on Native and Denatured Proteins. J. Biol. Chem. 157:621-625, 1945.

22. Laskowski, M.: Naturally Occurring Trypsin Inhibitors. *In*: Colowick, S. P., and Kaplan, N. O.: Methods in Enzymology. New York, Academic Press, Inc., 1955, Vol. II, pp. 36-54.

23. Kunitz, M.: Crystalline Soybean Trypsin Inhibitor. II. General Properties. J. Gen. Physiol. 30:291-310, 1947.

24. Hendley, C. D., Robbins, K C., Dertinger, B., Clements, G. R., and Ercoli, N.: Studies on Proteolytic Enzymes. I. Toxicology of Crystalline Trypsin and Chymotrypsin. Arch. Internat. Pharmacodyn. 106:164-177, 1956.

25. Tagnon, H. J., Weinglass, A. R., and Goodpastor, W. E.: The Nature and Mechanism of Shock Produced by the Intravenous Injection of Chymotrypsin. Am. J. Physiol. 143:644-655, 1945.

26. Shimkin, M. B., and Bierman, H. R.: Chymotrypsin in Cancer. Proc. Soc. Exper. Biol. and Med. 71:250-252, 1949.

27. West, P. M.: Ineffectiveness of Chymotrypsin Therapy in Malignancy. Proc. Soc. Exper. Biol. and Med. 71:252-253, 1949.

28. Barraquer, J.: Actual Results with the Enzymatic Zonulysis. Belfast, James Craig Lecture, 1959. Quoted by Schwartz, B., and Schwartz, J. B.: A Review of the Biochemistry and Pharmacology of Alpha-Chymotrypsin. Tr. Amer. Acad. Ophth. 64:17-24, 1960.

29. Bastian, W. J., Hill, R. G., and Ercoli, N.: Proteolytic Enzymes. III. Circulating Esterase Activities after Parenteral Trypsin and Chymotrypsin in Rabbits. Proc. Soc. Exper. Biol. and Med. 92:800-803, 1956.

30. Martin, G. J.: Anti-inflammatory Effect of Trypsin. Ann. N. Y. Acad. Sci. 68:70-87, 1957.

31. Auslander, M. M.: Serous Otitis Media - Treatment with Injectable Trypsin. Arch. Otolaryng. 67:24-27, 1958.

32. Ayvasian, J. H., Johnson, A. J., and Tillett, W. S.: The Use of Parenterally Administered Pancreatic Desoxyribonuclease as an Adjunct in the Treatment of Pulmonary Abscesses. Am. Rev. Tuberc. 76:1-21, 1957.

33. Maumenee, A. E.: Effect of Alpha-Chymotrypsin on the Retina. Tr. Amer. Acad. Ophth. 64:33-36, 1960.

VII INTERNATIONAL CONGRESS OF OTORHINOLARYNGOLOGY

PLEASE NOTE THE DATES: JULY 23 - 29, 1961

The Seventh International Congress of Otolaryngology will take place July 23-29, 1961, at Paris. The sessions will be held under the presidency of Professor Maurice Aubry at the New Faculty of Medicine, Rue des Saints-Pères.

The three official themes for discussion and the invited participants will be as follows:

1. Recent advances in the pathology and therapeutics of otosclerosis: Professors Sourdille, Sercer, Krmpotic, Weber, Ardouin, Larroude, Ferreri and Shambaugh.

2. Indications and five-year results of surgery and combined surgery and radiotherapy in the treatment of cancer of the larynx and the hypopharynx: Professors †Pietrantoni and Agazzi, Alonso, Casadesus, Jackson, Leicher, Leroux-Robert and Ormerod.

3. Comparisons of allergy and infections of the nose and the bronchi: Professors Van Dishoek, Clerici, Hlavacek, Voohorst, Mayer, Laskiewicz and Terracol.

Numerous gatherings and entertainments are planned for the members and their wives. At the close of the Congress various excursions will be arranged by Wagons-Lits Cook, 22 Rue de l'Arcade, the official travel agents who will also arrange transportation and hotel reservations.

A preliminary circular has been sent out, bearing a return coupon requesting full information as it is released. Those interested who have not received this circular should communicate *at once* with

Dr. Henry Guillon, Secretary General

6 Avenue Mac Mahon, Paris XVII, France.

ANNALS

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Executive Secretary: Dr. William L. Benedict, Mayo Clinic, Rochester, Minn.
Meeting: Palmer House, Chicago, October, 1960.

American Board of Otolaryngology

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Examination: Chicago, Oct. 3-6, 1960

American Broncho-Esophagological Association

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Secretary: Daniel C. Baker, Jr., M.D., 903 Park Ave., New York 21, N. Y.
Meeting: Lake Placid Club, Lake Placid, New York, May 23-24, 1961

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Meeting: Lake Placid, N.Y., May 26-27, 1961

VII International Congress of Otolaryngology

President: Prof. M. Aubry, Paris
Sec. Gen.: Dr. H. Guillon, 6 Ave. Mac-Mahon, Paris XVII France
Meeting: Paris, July 15-22, 1961

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